Magnetic resonance imaging in cardiac syndrome X

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ABSTRACT

BACKGROUND: Cardiac syndrome X is a subject with yet unsettled etiology and management. Conventional investigations have not been able to establish that chest pain is due to myocardial ischemia. Magnetic resonance imaging has higher resolution and is more accurate for detecting ischemia.

AIMS AND OBJECTIVES: To establish subendocardial ischemia as the cause of chest pain in cardiac syndrome X by virtue of stress perfusion cardiac MRI.

METHODS: Contrast enhanced cardiac MRI was performed in 15 cases and 7 matched controls both at rest and during a six minute infusion of adenosine. Both visual and quantitative analysis were performed. In quantitative analysis both myocardial perfusion index and myocardial perfusion reserve index was measured.

RESULTS: There was a significant increase in myocardial perfusion in both subendocardium as well as in subepicardium in both cases as well as in controls upon stress with adenosine. In controls the subendocardial perfusion index rose from 0.13 ± 0.3 to 0.18 ± 0.3 and in the subepicardium from 0.12 ± 0.2 to 0.18 ± 0.3 . In patients with cardiac syndrome X subendocardial perfusion index rose from 0.14 ± 0.3 to 0.19 ± 0.3 and subepicardial perfusion index rose from 0.13 ± 0.3 to 0.19 ± 0.3 . Visual analysis showed short lasting subendocardial dark rim artifacts in both cases and controls which lasted for only 3 to 5 beats.

CONCLUSION: Our cardiovascular MR study of patients with cardiac syndrome X demonstrated significant and almost similar magnitude adenosine induced increase in both subendocardial and subepicardial myocardial perfusion indices in both study as well as control group. We found no evidence of subendocardial ischemia in patients with cardiac syndrome X. JMS 2011;14(2):46-51

Key Word: Cardiac syndrome X, MRI, ischemia, subendocardium

Introduction

Angiography became widely applicable in 60's, and soon it was realized that about 20% of patients with anginal chest pain have normal coronary angiograms¹. KEMP in 1973 coined the term cardiac syndrome X for such patients². Some physicians regard this as sufficient to diagnose CSX, the so-called broad diagnosis of CSX³, however the classical definition of

cardiac syndrome X (CSX) stands as angina like pain on effort, ST segment depression on exercise stress test and normal coronary arteries at angiography in the absence of any other cardiac or systemic diseases (for example, hypertension or diabetes) known to influence vascular function⁴. Many studies have taken abnormal myocardial SPECT in place of exercise stress test, and have defined syndrome x as chest pain, normal coronaries, abnormal exercise ECG and/or reversible defects on myocardial SPECT^{5,6}. The pathophysiology of cardiac syndrome x has mainly centered around microvascular dysfunction, although abnormal pain perception has also been proposed by many studies. Numerous non invasive imaging studies have been carried out to determine whether ischemia is

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present. In the majority of patients, ventricular function under conditions of rest or stress - as assessed by radionuclide ventriculography⁷ or echocardiography⁸ has been normal. Thallium-201 myocardial-perfusion studies of patients with syndrome X have found abnormal results in a proportion of patients ranging from a few to the majority⁹. Some studies in which positron-emission tomography (PET) was used have shown abnormal heterogeneity in perfusion¹⁰, whereas others have shown no abnormalities¹². A global assessment of published data shows that metabolic evidence of stress induced myocardial ischaemia, including myocardial lactate production, coronary sinus oxygen desaturation and coronary sinus pH reduction, has clearly been obtained in at least a subgroup ($\geq 20\%$) of patients with CSX.⁴ Notably, in a recent study Buchthal et al by assessing myocardial phosphorus 31 metabolism by MR spectroscopy, showed typical metabolic ischaemic changes during a handgrip test in about 20% of women with CSX¹¹. More recent studies however, with stricter criteria for the selection of patients suggest that lactate production is normal in patients with syndrome X.¹² Cardiac MRI recently has been found to be accurate enough for detection of coronary ischemia. Panting *et al* in a cardiac MR study in 2002 demon-

presented with classical cardiac syndrome x. Fifteen cases and seven controls gave written informed consent out of screened fifty cases and ten controls. The study was completed in a period of two years w.e.f., Jan 2009 to Dec 2010. Inclusion criteria for cases were typical effort angina, positive exercise stress test (0.1 mV horizontal or downsloping ST-segment depression of 80 msec after the J point) and normal coronary angiogram, interpreted by two different observers. HTN, diabetes, dyslipidemia, LVH, valvular heart disease, cardiomyopathy, smoking were ruled out. Controls were healthy subjects with no history of chest pain. This study was approved by institutional ethical committee report. Echocardiography was done to rule out cardiomyopathy, LVH, valvular heart disease. Tread mill test required (bruce protocol was followed)-down sloping or horizontal ST segment depression of 1mm or more for 80 msec after J point. Coronary angiography - all routine views with additional (if necessary) were taken. Intracoronary ergonovine was used to rule out coronary spasm. Coronary angiogram was seen by two different observers to rule out epicardial coronary artery disease. Demographic characteristics of the cases and controls were almost similar (Table 1).

Table 1. Demographic characteristics of the saese and controls

	Demographic Characteristics								pvalue
	Study				Control				
	min	Max	Mean	SD	min	max	Mean	SD	
Age (yr)	47	66	56.8	4.9	50	56	54.1	2.0	0.117
Blood Sugar (F)	68	98	84.3	7.4	79	90	87.0	3.9	0.303
Blood Sugar (PP)	112	136	126.8	7.7	112	134	125.0	8.0	0.571
Total Cholestrol	132	200	160.4	20.1	100	154	138.0	18.1	0.018
Triglycerides	128	172	146.7	14.8	110	150	135.1	14.8	0.230
LDL	67	90	79.1	7.1	68	89	78.1	6.3	0.697
HDL	40	60	50.7	5.0	46	55	50.7	3.5	0.915
Systolic Blood Pressure	110	134	122.4	6.8	110	120	115.4	5.1	0.018
Diastolic Blood Pressure	70	86	78.5	5.6	70	80	73.1	4.1	0.039

strated subendocardial ischemia in patients with cardiac syndrome X¹³, another in 2007 found results contrary to the same¹⁴, but there were valid differences between the two on the basis of which the first study could not be negated. Patients with cardiac syndrome x roam around from physician to physician, may undergo multiple angiograms and change in treatment from time to time. We have undertaken this study to consolidate subendocardial ischemia as the cause for chest pain in cardiac syndrome X.

Material and Methods

This study was a prospective study conducted in collaboration by departments of Cardiology and Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir on patients who

FIGURE 1. Subendocardial Perfusion Index

FIGURE 2: Subepicardial Perfusion Index

FIGURE 3: Subendocardial Reserve Index

FIGURE 4: Subepicardial Perfusion Reserve Index

Cardiac MRI

Cardiovascular magnetic resonance imaging was performed with use of a 1.5-T scanner (SIEMENS, SINGO) that used a gradient-echo sequence with a 90-degree saturation pulse for T1 weighting. A cardiac phase-array receiver coil was used with sequence variables as follows: time to echo-1.2 msec; repetition time-3 msec; phase matrix-64; slice thickness-10 mm; Field of view-450 by 225 mm yielding a pixel size of 3.5 by 3.5 mm interpolated to 1.75 by 1.75 mm. The two-slice

sequence was started on the R wave for systolic gating and to ensure an adequate acquisition window during any adenosine-induced tachycardia. Studies were performed at rest and during a six-minute infusion of adenosine (140 μ g per kilogram of body weight per minute) to achieve intense coronary hyperemia. The two studies were separated by 20 minutes to allow equilibration of the contrast agent after the first injection. Two short-axis left ventricular slices were placed one third and two thirds of the distance from base to apex, with acquisition every cardiac cycle for 50 beats. A bolus of gadopentetate dimeglumine (0.05 mmol per kilogram) was injected at a rate of 5 ml per second for each first-pass study by means of a power injector. The images were analyzed quantitatively, in a masked fashion, and were presented in random order. Each series of images was analyzed by measuring the signal in regions of interest in the left ventricular blood pool and myocardium. For analysis, the myocardium was divided into subendocardial and sub-epicardial regions, which were drawn with the outer borders close to the endocardial and epicardial surfaces and with the inner borders adjacent to each other in the mid-wall. The analysis was performed with software designed in house. The regions of interest were drawn on a single image and propagated automatically throughout the perfusion series. Each image was then checked for positioning, and adjustments were made for any respiratory movement. The intervals between images were calculated from the electrocardiographic trace obtained during acquisition, and from these measurements, curves showing signal intensity plotted against time were constructed for each region of interest. An index of myocardial perfusion was then calculated with the use of myocardial slope measurements. Curve fitting was used to obtain the slope of the first-pass contrast enhancement for each of the myocardial regions of interest and the left ventricular blood-pool region of interest. The myocardial slope was then normalized by dividing it by the left ventricular blood-pool slope. This method compensates for changes in the input function caused by the effects of adenosine on heart rate and systemic circulation. The ratio of the myocardial perfusion index during stress to that with the subject at rest was defined as the myocardial-perfusion reserve index. Subepicardial perfusion and subendocardial perfusion were compared to determine the degree of heterogeneity across the myocardial wall. Transmural perfusion was assessed by combining the subepicardial and subendocardial regions of interest. Heterogeneity within the subendocardial regions of interest was assessed by visual scoring of 6 segments in each slice (total for the two slices, 12 segments).

In addition to undergoing magnetic resonance imaging, all subjects graded the level of pain associated with the adenosine infusion on the following scale. 1) no pain; 2)mild discomfort; 3)moderate but bearable pain; 4)severe pain; 5)the worst pain ever experienced.

Statistical Analysis

Data was described as mean $\pm$ SD and percentage. The inter and intra group comparisons were made by Mann

Whitney U test and wilcoxon signed rank test. p value of < 0.05 was considered significant. The software used was SPSS 11.5 and MS Excel.

Results

There was a significant increase in myocardial perfusion in both subendocardium as well as in subepicardium in both cases as well as in controls upon stress with adenosine.

In controls the subendocardial perfusion index rose from $0.13 \pm .03$ to $0.18 \pm .03$ and in the subepicardium from $0.12 \pm .02$ to $0.18 \pm .03$. In patients with cardiac syndrome x subendocardial perfusion index rose from $0.14 \pm .03$ to $0.19 \pm .03$ and subepicardial perfusion index rose from $0.13 \pm .03$ to $0.19 \pm .03$.

Subendocardial perfusion reserve index and subepicardial perfusion reserve index were 1.35 ± 0.25 and 1.45 ± 0.13 respectively in cases and 1.44 ± 0.040 and 1.49 ± 0.27 respectively in controls.

Subendocardial/subepicardial perfusion reserve index was 0.94 ± 0.20 in cases and 1.01 ± 0.37 in controls.

Transmural perfusion reserve index was 1.39 ± 0.12 in cases and 1.44 ± 0.23 in controls.

Visual analysis showed short lasting subendocardial dark rim artifacts in both cases and controls which lasted for only 3 to 5 beats.

Chest pain in response to adenosine was seen in both cases as well as controls.

Visual analysis

Upon visual analysis we found that most of the patients as well as controls showed initial subendocardial signal reduc-

tions on the first-pass cardiovascular MR images, which disappeared after approximately three to five heartbeats.

Discussion

Both the cases and controls in our study showed a significant perfusion response of almost similar magnitude in response to adenosine in both the subendocardium and subepicardium. We therefore found no evidence of subendocardial ischemia in our patients with cardiac syndrome X.

Subendocardial perfusion index in our study increased from rest to stress in patients with syndrome x from $0.14 \pm .03$ to $0.19 \pm .03$ & in controls from 0.13 ± 0.03 to 0.18 ± 0.03 . This is in contrast to a previous study¹³ where subendocardial perfusion in patients with syndrome X did not increase significantly in comparison to controls, and in accord with a previous study¹⁴ where subendocardial perfusion increased significantly in response to stress with adenosine in patients with syndrome X. Both our study and the study by Panting *et al* and the study by Vermeltfoort *et al* showed a significant and a similar magnitude of increase in subepicardial perfusion.

Characteristics of our patient group were almost similar to the control group with an insignificant p value in all characteristics. These characteristics were also almost similar to the study group and the control group who participated in the study by Panting *et al*. We used the same definition of cardiac syndrome X as that in the study by Panting *et al*. This definition has been used by almost 42 studies out of 57 studies so far published pubmed from 2003 to 2008¹⁵. Vermeltfoort *et al*¹⁴ in their study used the definition of cardiac syndrome as exertional angina; an abnormal exercise electrocardiogram suggesting

FIGURE 5: Short lasting Gadolinium enhanced first pass perfusion defects seen in short axis left ventricular cuts during first three to four beats (A-D) and subsequent disappearance

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. However, the selection of syndrome X patients using both exercise-ECG and SPECT is an accepted method used by almost 11 studies on cardiac syndrome X so far¹⁵.

In our study we found dark rim artifacts during the peak gadolinium concentration in the left ventricular blood-pool MRI images in most of the patients in both the study and control group. These artifacts were very short lasting. They were seen for initial 4-5 beats with rapid disappearance later. This temporary signal loss is considered to be an artifact 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.^{16,17} Several causes have been proposed for this so-called dark rim artifact, 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, it is not to be expected that we experienced more artifacts compared to the study of Panting *et al.*¹² Similar short lasting artifacts were found in all patients in the study by Vermeltfoort *et al.*¹⁴.

Chest pain in response to adenosine ranging from mild to severe was found in almost all the patients in both the study and control groups in our study, although a higher grade of pain was found in study group. Severe pain in response to adenosine has been found in healthy volunteers in many studies and in 86% of patients with cardiac syndrome X in the study done by Vermeltfoort *et al.*, in whom no evidence of subendocardial ischemia was found either by visual assessment or quantitative analysis on cardiac MRI. Adenosine is known to cause chest pain in healthy volunteers but this higher grade of pain in response to adenosine in patients with cardiac syndrome X in our study and the study by Vermeltfoort *et al.* might mean an abnormal pain perception in these patients. This enhanced pain perception in response to adenosine has been found in other studies as well¹⁸.

In our study we did not find any evidence of microvascular dysfunction in either subendocardium or epicardium in patients with syndrome X, as both the study and control groups showed a clear increase of almost similar magnitude in myocardial perfusion index in response to adenosine.

The pathogenesis of cardiac syndrome X is unclear. The main hypotheses for its occurrence are microvascular dysfunction or abnormal pain perception. There have been conflicting data concerning the possible role of myocardial ischaemia in syndrome X. Several studies of patients with syndrome X demonstrated ischaemia whereas other investigations found no confirmatory evidence of ischaemia during stress in these patients. Alternative non-ischaemic mechanisms of chest pain have been proposed in patients with cardiac

syndrome X. Panza *et al.* by virtue of radionuclide angio, thallium stress and dobutamine stress echo found evidence against ischemia in syndrome X¹⁹. Camici *et al.* found normal myocardial metabolism and LV functions upon incremental pacing in cardiac syndrome X²⁰. Shapiro *et al.*²¹ Chauhan *et al.*²² found abnormal pain perception to catheter induced right atrial stimulation. Cannon RO 111²³ found abnormal pain perception to catheter manipulation and pacing. Pasceri *et al.*²⁴ detected abnormal pain perception to electrical stimuli. Lanza *et al.*²⁵ found abnormal cardiac adrenergic function. Fedel *et al.*²⁶ and Rosen D *et al.*²⁷ found evidence in favour of abnormal central neural handling of painful stimuli.

The exact mechanism of chest pain in patients with syndrome X remains unclear since our data does 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.

Conclusion

We conclude that our cardiovascular MRI study of patients with chest pain, positive exercise ECG stress testing, and normal coronary angiography, demonstrated significant and of almost similar magnitude adenosine-induced increases in both subendocardial and subepicardial MPIs in both study and control groups. We found no evidence for specific subendocardial ischaemia with MRI in the study group of patients.

Future directions

Taking into account various studies so far done on cardiac syndrome X, there is a possibility that its pathogenesis may be heterogenous. we advocate that larger studies taking into account various different groups of patients and using different stress protocols for cardiac MRI in these patients may elucidate the cause of chest pain in cardiac syndrome X.

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