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Utility of serum miRNAs profile in patients with Cardiac Syndrome-X

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Abstract

Objective: We investigated the plasma levels and utility of miR-126, miR-208 and miR-146a in patients with cardiac syndrome-X (CSX). **Patients and methods:** The study included 54 patients (49.5 ± 9.9 years of age) with CSX (typical chest pain, positive exercise stress test, and normal coronary angiograms) and 32 age and sex matched control subjects. Endothelial function was assessed utilizing brachial flow mediated (FMD) and nitroglycerine flow mediated dilation (NMD). RNA was extracted and isolated from the sera and miRNA-126, miR-208 and miRNA-146a levels were detected by fluorescent quantitative polymerase chain reaction. **Results:** FMD was significantly decreased in patients with CSX compared to controls, associated with significant increase in hs-CRP, IL-6 and TNF-α. miR-126 expression was significantly decreased in CSX patients compared to controls ($P<0.001$), whilst miR-208 and 146a expressions were significantly increased ($P<0.001$). The dysregulation of the three miRNAs were significantly correlated with the degree of endothelial dysfunction ($P<0.001$ for all). Moreover CSX patients with impaired myocardial perfusion (IMP) had a significantly downregulation in miR-126 whilst both 208 and 146a were significantly upregulation ($P<0.001$) compared to those with normal myocardial perfusion. Of note miR-126, miR-208 and miR-146a have a good discrimination in predicting IMP in patients with CSX. **Conclusion:** The current study indicated that serum miR-126, miR-208 and miR-146a are significantly deregulated and correlated with endothelial dysfunction in CSX patients. They were independent markers of myocardial perfusion in CSX patients and might be of great predictive value in risk stratification of patients with syndrome-X.

Keywords: MicroRNAs, cardiac syndrome-X, endothelial function.

Introduction

Cardiac syndrome-X (CSX) is considered generally as a clinical condition with good prognosis. However several studies demonstrated that patients with CSX and associated with endothelial dysfunction had a significant risk for adverse outcome. **(**Hurst **et al. 2006)** The pathophysiological mechanisms of CSX is not clearly understood and have been the subject of great interest for decades **(**Sari**, et al, 2008).**

Although CSX has been recognized for more than three decades, it remains underappreciated as a distinct clinical entity **(**Kemp**, 1973).** Multiple pathophysiological abnormalities have been proposed in patients with CSX, including reduced coronary flow reserve, abnormal pain perception, endothelial dysfunction, and altered adrenergic activity, parasympathetic impairment and increased platelet

aggregability. Convincing evidence indicated that microvascular ischemia related to impaired endothelial function is the underlying pathophysiological explanation for CSX **(**Chauhan**, 1994;** Egashira, et al 1993 Chauhan-b, 1994 Frobert et al, 1995; Gulli, et al, 2001; Lanza, et al, 2001**).**

Several studies showed promising results for the use of circulating microRNAs as potential biomarker in patients with acute coronary syndromes, stable coronary artery disease,, heart failure. However, whether CSX is associated with changes in microRNAs expression pattern is unknown. The objective of this study was to investigated the plasma levels and utility of miR-126, miR-208 and miR-146a in patients with cardiac syndrome-X (CSX).

Subjects and Methods

Fifty four patients [29 (54.2%) males and 25 (45.8%) females]; with a mean age of 49.5±9.9 years. with cardiac syndrome-X were enrolled to the study. The subjects had typical anginal pain on effort, ST segment depression on exercise stress test (positive stress test) and normal coronary arteries at angiography. The exclusion criteria for all subjects were a previous history of cardiac disease (e.g., myocardial infarction, heart failure, cardiac arrhythmias, pacing, and cardiomyopathy), known history of leukopenia, thrombocytopenia, malignancy, severe hepatic or renal dysfunction, surgery or skeletal muscle damage, and evidence for inflammatory disease. In addition, 32 healthy adult volunteers (normal electrocardiogram and no history of cardiovascular diseases) were enrolled in this study as a control group.

Non-invasive endothelial function assessment was performed with evaluation of flow mediated dilatation and nitroglycerin mediated dilatation as previously described by Celermajer, et al (1990).

Coronary angiography: All patients with CSX underwent selective coronary artery angiography. The TIMI frame count was used for the quantification of coronary blood flow for each major coronary artery in each patient by an observer blinded to the study **(**Gibson**, et al; 1996).** Myocardial blush (MBG) was graded using the method described by van't Hoff et al (van't, et al; 1998) (MBG = 0 when no contrast density is present, MBG = 1 when minimal contrast density is present, MBG = 2 when moderate to less-than normal contrast density is present, and MBG = 3 when normal contrast density is present). Impaired myocardial perfusion was defined as a MBG score of less than 3, and normal myocardial perfusion was defined as an MBG score of 3 in all coronary territories (Atmaca, et al, 2005 and Oykay, Cengel, et al; 2007).

Biochemical Measures

The blood samples of patients CSX and healthy subjects were collected and plasma was isolated by centrifugation and conserved at -80°C until purification. The total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-c) concentrations were determined enzymatically. The low-density lipoprotein cholesterol (LDL-c) level was assayed using an indirect method. Interleukin-6 and TNF-α and CRP were measured with high-sensitivity enzyme linked immunoassay with the Human Basic Kit FlowCytomix (BMS8420FF, eBioscience, USA) and the Human FlowCytomix (Simplex BMS8213FF and BMS8288FF, eBioscience, USA) on a BD FACSCalibur instrument (BD Biosciences, USA) according to the manufacturer's instructions **(** Nagueh, et al, 2009) .

Detection and analysis of miRNAs by qRT-PCR

Utilizing real-time quantitative reverse-transcription polymerase chain reaction (qRT-PCR) to determine the expression of miRNAs. First, reverse transcription was then performed using the previously obtained RNA (TaqMan miRNA reverse transcription kit, Invitrogen). according to the manufacturer's instructions with an RT-PCR system (Bio-Rad, USA). Second, 2 μL of cDNA was used as the template for qRT-PCR. Plasma miR-126, miR-208 and miR-146a expression was detected using SYBR Green miRNA qRT-PCR kits according to the manufacturer's protocol and a 7300 Real-Time PCR System (Applied Biosystems, CA, USA). A melting curve analysis was performed at the end of the PCR cycle to validate the specificity of the expected PCR product. We studied the following miRs: miR-126, miR-208 and miR-146a. The quantification and relative expression of the studied miRs was assessed with the delta-Cp technique (Roche) with c-elegans-39 serving as the internal standard **(**Mitchell, et al, 2008 and Fichtlscherer, et al; 2010) Each sample from each study subject was analyzed by PCR in triplicate. The relative expression level of each miRNA was computed using the comparative CT method, which was defined as $2^{-\Delta Ct}$, where ΔCt ╒ (Ct miRNA of sample x − Ct miR-156a of sample x). To reduce the number of false positives, only measured miRNAs

whose expression in CSX patients differed from the control subjects by more than 2-fold on average.

Statistical analysis

A widely used method to present relative expression of miRNA is the $2^{-\Delta\Delta ct}$ method. Relative expression of miRNA presents the data of the miRNA of interest ($Ct_{miRNA\ of\ interest}$) relative to internal control gene ($Ct_{internal\ control\ miRNA}$), termed Δct. Results are calculated as Δct± standard deviation (SD). Independent-sample T test was used for 2-group comparisons. For categorical variables, Chi-Square test was used. Differences were considered statistically significant at a value of P<0.05.. ROC analysis was used to assess the diagnostic accuracy of each circulating miRNA for all the groups. The area under the ROC curve (AUC) was considered a diagnostic index, and the best cut-off point was obtained based on the highest sensitivity and specificity values. All the tests were 2-sided, and differences with $p<0.05$ were considered to be statistically significant.

Results

The demographic data of the participants are presented are summarized in table 1. Patients with CSX and normal subjects were all matched for age, sex, body mass index, systolic and diastolic blood. Moreover fasting blood sugar, total cholesterol, total triglycerides, HDL-c and LDL-c and serum creatinine were comparable. The inflammatory markers (hs-CRP, IL-6 and TNF-α) were significantly higher in CSX patients compared to controls (P<0.001). Flow mediated dilation was significantly decreased in CSX patients compared to controls (P<0.001), while the nitroglycerin mediated dilatation (NMD) was comparable among both groups.

Table (1): Demographic characteristics of studied subjects

Variables	Cardiac syndrome-X n=54	Control group n=32	P value
Age (years)	49.5 ± 9.6	47.2 ± 8.5	0.681
BMI	25.32 ± 2.85	24.15 ± 2.11	0.247
SBP (mmHg)	142 ± 14	135 ± 11	0.09
DBP (mmHg)	85 ± 7	82 ± 5	0.163
Glucose (mg/dl)	98.70 ± 18.25	91.30 ± 18.12	0.117
TC (mg/dl)	176.19 ± 17.25	169.53 ± 19.13	0.103
TG(mg/dl)	135.16 ± 31.20	127.17 ± 33.36	0.115
HDL-c (mg/dl)	41.72 ± 7.22	43.21 ± 7.11	0.351
LDL-c (mg/dl)	101.16 ± 19.22	98 ± 23.10	0.266
VLDL-c (mg/dl)	25.27 ± 7.02	23.99 ± 7.23	0.139
SC (mg/dl)	0.81 ± 0.22	0.87 ± 0.19	0.295
BU(mg/dl)	21.92 ± 7.26	22.01 ± 6.14	0.225
TNF-α (pg/ml)	6.18±1.62	1.75±0.42	<0.001
hs-CRP ug/mL	6.38±2.25	1.29+0.07	<0.001
IL-6(pg/ml)	7.85±1.9	2.91±0.85	<0.001
miR-126	3.45+0.76	0.79 ± 0.34	<0.001
miR-208b	0.81±0.32	3.75±0.61	<0.001
miR-146a	0.75±033	3.91±0.42	<0.001
FMD%	10.25 ± 6.72	21.35 ± 7.95	<0.0001
NMD%	26.15 ± 7.19	28.35 ± 9.11	>0.05

Patients with CSX were classified into two groups according to the TIMI frame count (group with impaired myocardial perfusion [37 patient], and a group of normal myocardial perfusion 17 patients). The data of TIMI frame count are represented in table-2. FMD was significantly lower in IMP patients compared to those with NMP (P<0.01). At the same time the inflammatory biomarkers were significantly higher in CSX patients **(P<0.001)**.

Table (2): Comparison of TIMI frame counts in patients with cardiac syndrome-x with and without impaired myocardial perfusion.

Major epicardial coronary artery	CS X (IMP)	CS X (NMP)	P value
Left anterior descending coronary artery	39 ± 15	21 ± 6	<0.001
Left circumflex coronary artery	27 ± 11	17 ± 5	<0.001
Right coronary artery	21 ± 8	14 ± 5	<0.004

The expression levels of circulating miRNAs in the studied population

The levels of plasma miR-126 in patients with CSX was 5.43 lower than that of control subjects (P<0.001), whilst levels of miR-208 and miR-146a were 4.45 fold and 4.62-5.52 fold higher in patients with CSX compared to control subjects respectively (P<0.001 for all) [Table-1 and figures: 1-A; 2-A & 3-A].

The plasma levels of miR-126 was significantly (1.59-fold) lower in patients with IMP compared to those with NMP (P<0.01) [Table-2 and figure:1-b]. On the other hand the plasma levels of both miR-208 and miR-146a were significantly (1.61-fold and 1.45-fold respectively) higher in patients with IMP compared to those with NMP (P<0.03 for both) [table-3 and figures: 2-B and 3-B].

Table (3): Comparisons of patients with CSX with impaired myocardial perfusion versus CSX patients with normal myocardial perfusion

Variables	CSX with Impaired MP N=37	CSX with normal MP N=17	P value
SBP (mmHg)	143.28 ± 15.30	137.18 ± 11.70	0.09
DBP (mmHg)	82.92 ± 10.46	76.81 ± 8.46	0.09
Glucose (mg/dl)	77.78 ± 21.31	85.78 ± 22.45	0.211
TC (mg/dl)	176.96 ± 15.27	176.78 ± 20.67	0.177
TG(mg/dl)	134.21 ± 36.79	135.53 ± 43.41	0.721
HDL-c (mg/dl)	42.60 ± 8.10	43.31 ± 7.31	0.459
LDL-c (mg/dl)	113.00 ± 18.71	107.56 ± 20.91	0.627
VLDL-c (mg/dl)	26.10 ± 7.10	25.75 ± 8.16	0.635
SC (mg/dl)	0.89 ± 0.20	0.84 ± 0.17	0.513
BU(mg/dl)	22.21 ± 7.30	23.03 ± 6.50	0.441
TNF-α (pg/ml)	8.16±2.75	4.99±1.63	<0.004
Hs-CRP (ml)	8.83±2.98	5.39±2.11	<0.004
IL-6(pg/ml)	8.73±2.37	5.12±1.92	<0.003
miR-126	0.76±0.52	2.45±0.39	<0.01
miR-208	3.44±0.37	2.036±0.31	<0.3
miR-146a	3.70±0.38	2.49±0.35	<0.03
FMD%	8.75 ± 6.72	22.35 ± 8.75	<0.001
NMD%	24.45 ± 7.13	28.25 ± 9.33	0.118

FMD: Flow-mediated dilation; NMD: Nitroglycerine-mediated vasodilatation

Association between miRNAs deregulation and endothelial function are summarized in table 4 and figure 4: A, B & C.

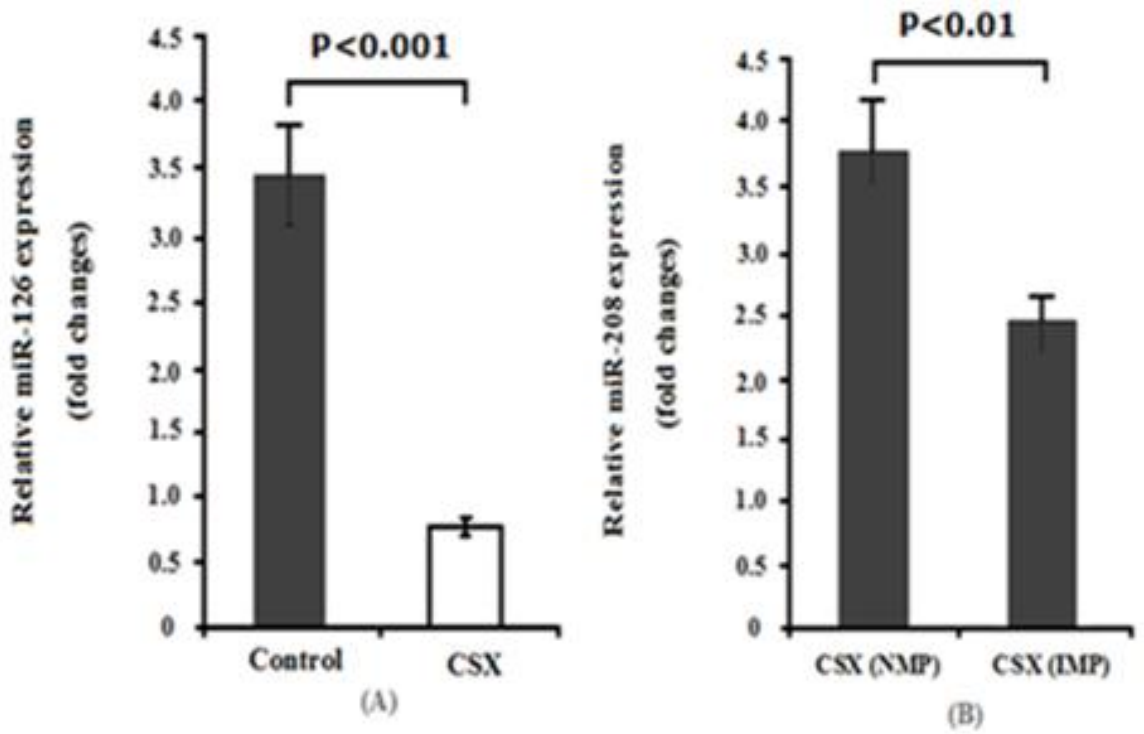

Figure-1 Expression of levels of plasma miR-126 in patients

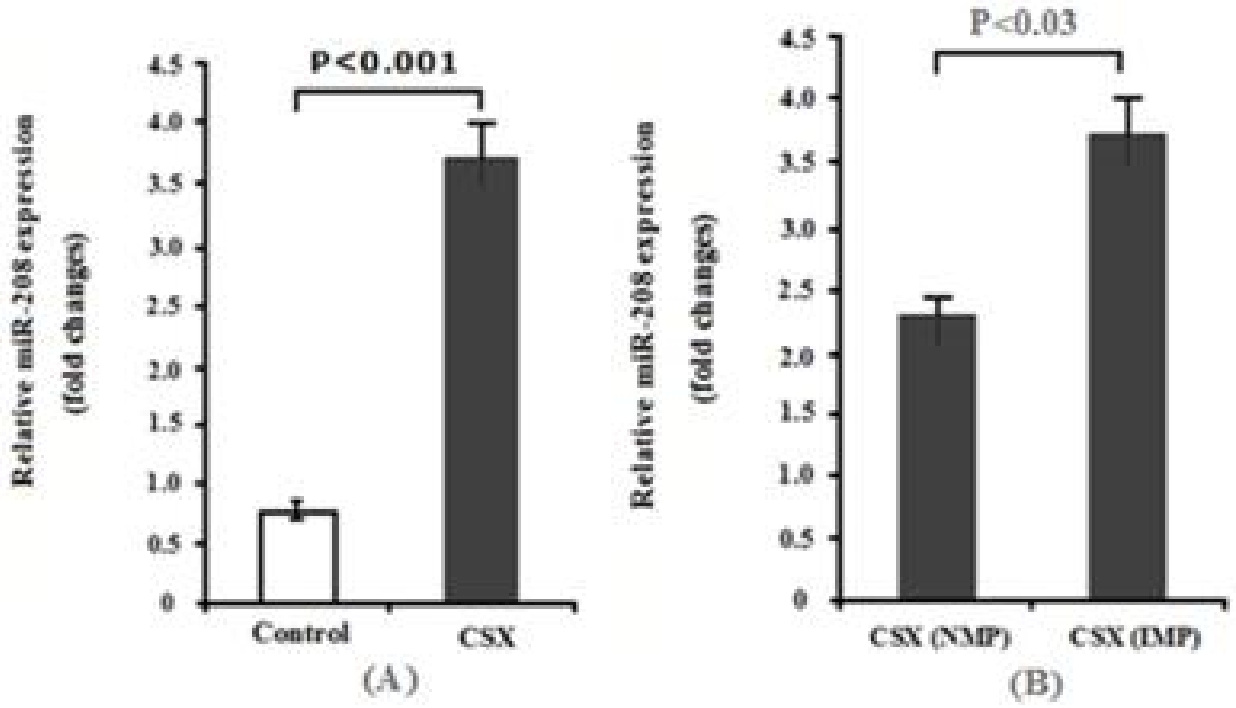

Figure-2 Expression of levels of plasma miR-126 in patients

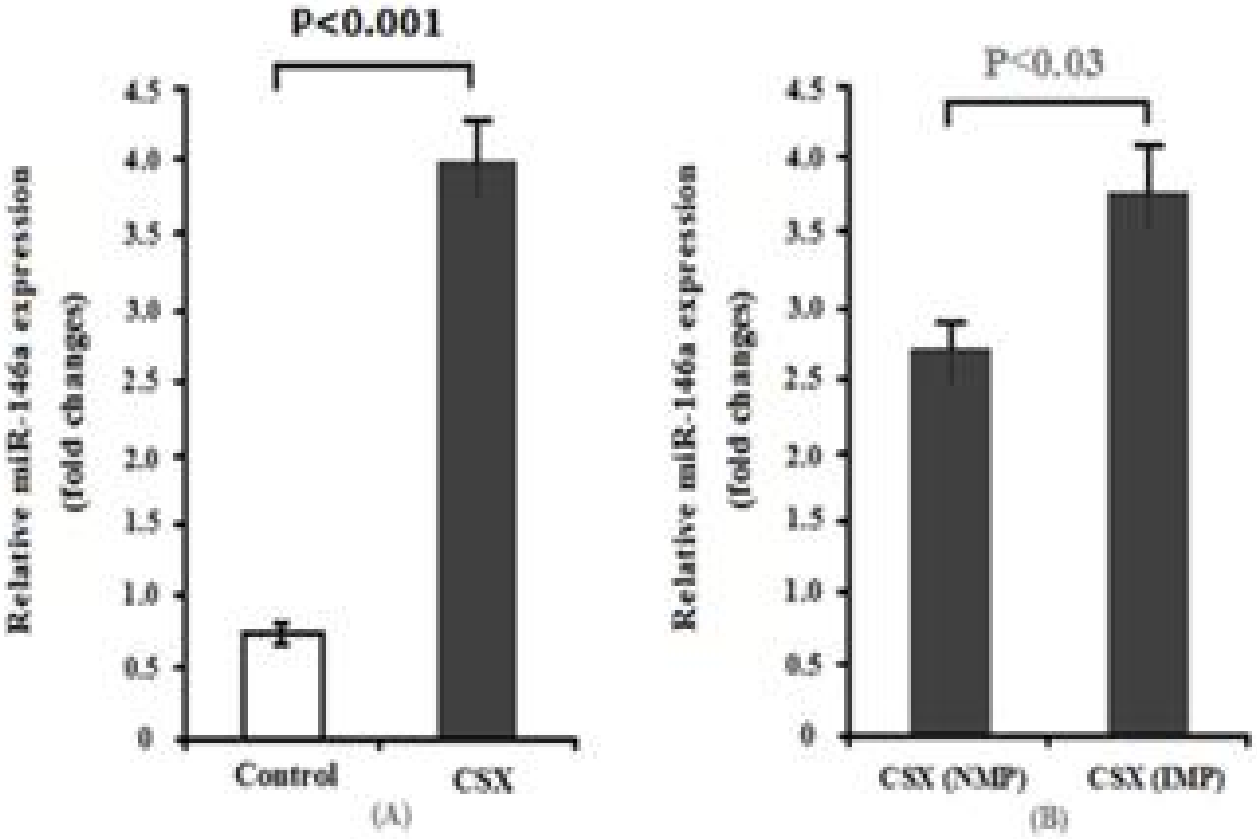

Figure-3 Figure-2 Expression of levels of plasma miR-126 in patients

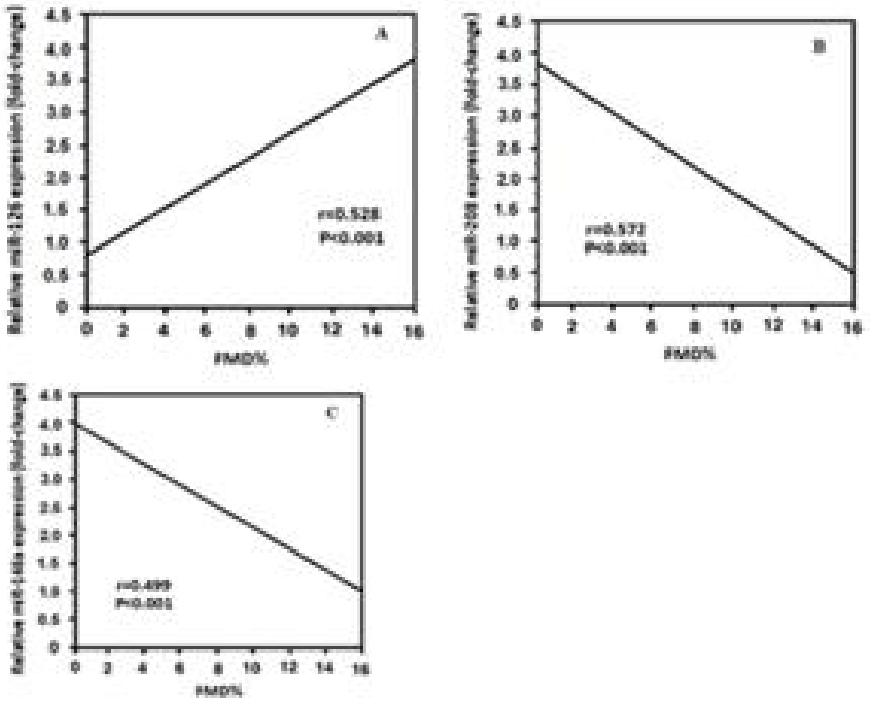

Figure-4 Association between miRNAs deregulation and endothelial function

Table (4): Correlation between myocardial perfusion and blood biomarkers in patients with cardiac syndrome-X.

Marker	r	p
miR-126	0.73	0.001
miR-208	0.58	0.001
miR-146a	0.65	0.001
Hs-CRP	0.11	0.3
IL-6 (pg/ml)	0.10	0.09
TNF-α (pg/ml)	0.14	0.06
TC (mg/dl)	0.21	0.07
Triglycerides (mg/dl)	0.19	0.07
HDL cholesterol (mg/dl)	0.15	0.21
LDL cholesterol (mg/dl)	0.17	0.08

Role of plasma miRNAs in predicting impaired myocardial perfusion in patients with CASX.

To examine the utility of of miRNAs (miR-126, miR-208, and miR-126a) as biomarkers for predicting IMP in patients with CSX, ROC analysis was performed on all 54 with CSX. The ROC curves of plasma miR-126, miR-208 and miR-146a levels revealed strong discrimination between those with IMP from those with NMP patients, with AUCs of 0.951, 0.942 and 0.955, respectively [figures-5: A, B, C]. These results indicated that plasma miR-126, miR-208 and miR-146a might be valuable biomarkers for risk stratification of patients with CSX. The AUCs, maximum cut-off points, sensitivities, specificities, and *p*-values of the circulatory miRNAs (miR-126, miR-208, and miR-146a are summarized in table-5.

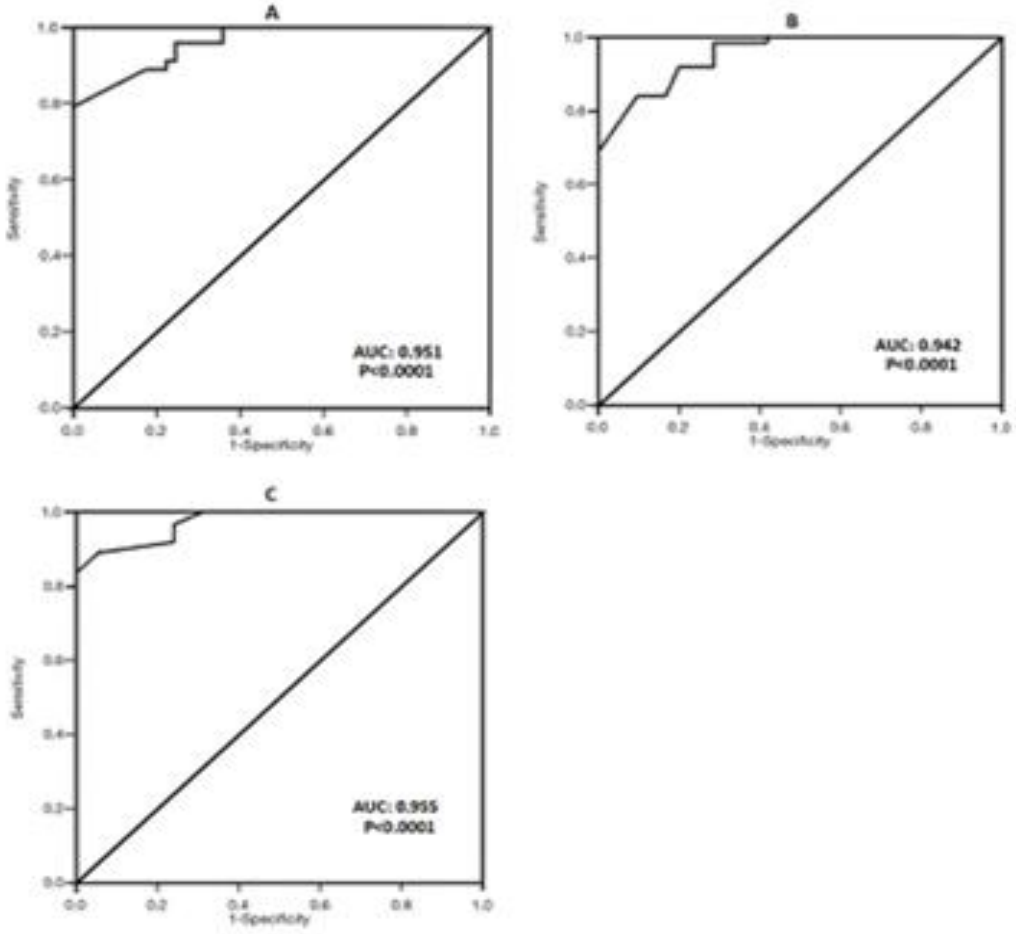

Figure-5 ROC curves of plasma miR-126, miR-208 and miR-146a levels

Table (5): Receiver operator characteristic curve (ROC) analysis of miRNA ratios for predicting impaired myocardial perfusion in patients with cardiac syndrome-X.

miRNA	AUC	Cut-off point	Sensitivity	Specificity	p-value
miR-126	0.951	2.75	81%	96%	<0.0001
miR-208	0.942	3.42	79%	95%	<0.0001
miR-146a	0.955	3.35	83%	97%	<0.0001

AUC, area under the curve.

Discussion

Our study demonstrates that patients with CSX were significantly associated with distinct dysregulation of miRNAs in the circulation. It is of note that CSX is associated with elevation in the inflammatory markers (hs-CRP, TNF-α and IL-6). Meanwhile these dysregulation were significantly correlated with impaired FMD.

The most significant finding was that plasma levels of miR-126 were down-regulated in CSX patients, while plasma levels of miR-208 and miR-146a were significantly upregulated in those patients. The significant association between the studied miRa in the current study and the inflammatory markers (hsCRP, IL-6 and TNF-α) coupled with significant decreasein FMD, could signal the significant role of these miRs deregulation in the pathogenesis of clinical profile of patients with CSX.

Okyay,et al (2015) found a significant association between inflammation and CSX. As they observed higher levels of NLR (an inflammatory marker) in patients with CSX, compared to control subjects, and demonstrated a significant association between NLR and impaired myocardial microcirculation.

The pathophysiology of CSX has not been clearly identified yet, although multiple abnormalities including abnormal coronary flow reserve, insulin resistance, abnormal autonomic control, enhanced sodium hydrogen exchange activity, abnormal cardiac sensitivity, microvascular spasm, endothelial dysfunction, oxidative stress, and silent atherosclerosis have been reported **(** Al Suwaıd **et al, 2001;** Hurst **et al, 2006;** Luo **et al, 2012;** Recıo-Mayoral **et al, 2013).**

Atherosclerosis preferentially occurs in arterial regions exposed to disturbed flow, in part, due to alterations in gene expression. MicroRNAs (miRNAs) are small, noncoding genes that post-transcriptionally regulate gene expression by targeting messenger RNA transcripts. Promising data indicates that disturbance of flow conditions regulate expression of miRNAs in endothelial cells both in vitro and in vivo. These flow-sensitive miRNAs, known as mechano-miRs, regulate endothelial gene expression and can regulate endothelial dysfunction and atherosclerosis. **(Kumar et al, 2014).**

Data concerning, whether the miRNAs expressions are altered or stay relatively stable with coronary artery diseases still controversy. While Fichtlscherer et al **(2010)**, found significant reductions in most absolute and relative endothelial-related miR expressions (miR-17, miR-92a, and miR-126) with increases in myocardial and inflammatory-related miRs (miR-133, miR-145, and miR-155) in patients with stable coronary artery disease, De Rosa et al **(2011)**, found little to no change in miR levels with stable coronary artery disease, but marked changes in some of theses miRs expression with acute coronary syndrome.

MiR-126 is considered the prototype of an endothelial-specific miRNA. It is highly expressed in vascularized tissues, endothelial cells and hematopoietic stem cells. Interestingly, it is known as Vascular Endothelial-statin (VE-statin), which is mostly expressed in endothelial cells and involved in vascular tubulogenesis . The role of miR-126 in vascular integrity and angiogenesis was demonstrated by targeted deletion of miR-126 in mice **(**Suarez **et al , 2008)**. It was observed that miR-217 and miR-146a regulate senescence in human umbilical vein endothelial cells (Harris**, et al; 1990)**

Fichtlscherer , et al (2010), reported that miR-208a have been shown to be elevated in patients with stable coronary artery disease, while Ren, et al; 2013), found a significant elevation in patients with acute coronary syndrome.

The current study demonstrated that the deregulation of all three miRNAs were significantly correlated with

endothelial dysfunction (significant decrease in FMD) differed from mildly impaired endothelial function to severe impairment in patients with CSX associated with significant dysregulation in miR-126; miR-208 and miR-146a, might signify the role of miRNAs in the pathogenesis of endothelial dysfunction in patients with CSX.

Vasa-Nicotera , et al; (2011) demonstrated that , endothelial-enriched miR-126, members of the miR-17/92a cluster (miR-17, miR-20a, and miR-92a), was significantly downregulated in the patient with stable coronary artery disease. In contrast they observed that these expressions were significantly upregulated with vulnerable coronary diseases.

The results revealed that there were significant down-regulation in circulating miR-126, and significant up-regulation in miR-208 and miR-146a levels in the plasma of CSX patients with IMP compared to those with normal myocardial perfusion. The data provide an evidence of the role of the dysregulation in the studied miRNAs for the discrimination utility in predicting patients with CSX with impaired myocardial perfusion from those with normal myocardial perfusion.

The data of our study showed that patient selection, age, gender, total triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, creatinine, systolic blood pressure, diastolic blood pressure, history of diabetes and smoking status was comparable among studied population. levels. This suggested that miR-126, MR-208 and miR-146a were potential biomarkers for CSX.

Limitations of the study include: Firstly, the present study represents a single-center study using a small sample size of patients with CSX, secondly, measurement of plasma miRNAs requires qRT-PCR, which is expensive and time-consuming. Therefore, less expensive and newer techniques to detect plasma miRNAs levels more rapidly can be expected in the near future.

In summary, we found a significantly deregulation of (miR-126, miR-208 and miR-146a) associated with endothelial dysfunction in patients CSX. Meanwhile the study demonstrated that the deregulation of miRNAs has a significant discrimination utility in predicting impaired myocardial perfusion in patients with CSX. The present study suggested that miR-126, miR-208 and miR-146a can be used as useful potential biomarker for prognosis and risk stratification of patients with cardiac syndrome-X.

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