

CORRELATION OF MEAN PLATELET VOLUME IN PATIENTS WITH CARDIAC SYNDROME X IN INDIAN POPULATION

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ABSTRACT

Platelets play a pivotal role in the development of atherosclerotic lesions, plaque destabilization and atherothrombosis. The methods of testing platelet activity can be time-consuming, expensive and technically difficult. Unlike more expensive or time-consuming methods of assessing platelet function, the determination of platelet size by quantification of Mean Platelet Volume (MPV), using automated haemograms, is simple and inexpensive. "Cardiac syndrome X" characterized with 1. Angina or angina-like chest pain, 2. ST segment depression that can be induced by treadmill exercise testing, 3. Normal coronary arteriography. As cardiac syndrome X and angina pectoris caused by typical obstructive coronary heart disease should be distinguished from each other for effective treatment. Although there has not been a clear explanation of the exact pathophysiological mechanism underlying cardiac Syndrome X, studies are suggestive that coronary micro-circular abnormalities and endothelial dysfunction play a role in the aetiology of the disease. Atherosclerosis and endothelial vasomotor dysfunction have been suggested as possible contributing factors. There are limited datas in literature to compare the MPV in cardiac syndrome X. This study was designed to compare MPVs of patients with Cardiac syndrome X, patient with CAD and of normal controls.

METHODS

Nine hundred and forty four patients who had undergone coronary angiography between May 2014 and April 2016 in Rajarajeshwari Medical College and Hospital, Bangalore, were retrospectively examined. Of these, 118 patients were enrolled in the study and were divided into three groups. The Cardiac Syndrome X group consisted of 40 subjects (18 men and 22 women with mean age group 45+4.2 years). The CAD group consisted of 33 subjects (18 men and 15 women with mean age of 46+4.8 years) with CAD, which was defined as >50% stenosis in a minimum of one coronary artery. The control group consisted of 45 age and sex matched individuals (23 men and 22 women with mean age of 45+4.5 years) who presented with chest pain, normal coronaries and no ischaemia during treadmill exercise testing.

RESULTS

The primary characteristics of the study population are given in Table 1. There was no statistical significance between the three groups with respect to age, sex, smoking or alcohol consumption (p = NS). There were no statistically significant differences in the MPV measurements between the cardiac syndrome X group and CAD groups. (Mean MPV 12.2±1.4 fL vs. 13.8±2.1 fL, p=NS). The MPV was significantly higher in both Cardiac syndrome X (mean = 12.2±1.4 fL) and CAD group (mean = 13.8±2.1 fL) compared with the control groups (mean = 7.9±1.1 fL) (p <0.01).

CONCLUSION

Elevated MPVs may participate in the pathogenesis of Cardiac Syndrome X. Prospective, placebo-controlled studies with large sample sizes that use multivariable survival analyses and long-term follow-up periods are required for the clinical evaluation of the prognostic value of increased MPV in patients with Cardiac Syndrome X.

KEYWORDS

Cardiac Syndrome X, Mean Platelet Volume, Coronary Artery Disease.

HOW TO CITE THIS ARTICLE: Raj RA, Kothari Y, Bewoor K, et al. Correlation of mean platelet volume in patients with cardiac syndrome X in Indian population. J. Evolution Med. Dent. Sci. 2016;5(62):4323-4326, DOI: 10.14260/jemds/2016/987

INTRODUCTION

Platelets play a pivotal role in the development of atherosclerotic lesions, plaque destabilization and athero-

thrombosis.¹ The methods of testing platelet activity can be time-consuming, expensive and technically difficult.² Unlike more expensive or time-consuming methods of assessing platelet function, the determination of platelet size by quantification of Mean Platelet Volume (MPV) using automated haemograms is simple and inexpensive.³ The biologic rationale linking MPV to clinical outcomes along with its universal availability has made it a promising indirect marker of platelet reactivity. MPV is a marker of platelet size and activity and a predictor of cardiovascular risk.⁴

Kemp⁵ in 1973 coined a term "cardiac syndrome X" with the following three characteristics: 1. Angina or angina-like chest pain, 2. ST segment depression that can be induced by

Financial or Other, Competing Interest: None.

Submission 11-07-2016, Peer Review 23-07-2016,

Acceptance 26-07-2016, Published 02-08-2016.

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DOI: 10.14260/jemds/2016/987

treadmill exercise testing, 3. Normal coronary arteriography. As cardiac syndrome X and angina pectoris caused by typical obstructive coronary heart disease should be distinguished from each other for effective treatment. In diagnosis of non-cardiac origin such as oesophageal disorders or psychiatric condition should be considered and ruled out. Although, there has not been a clear explanation of the exact pathophysiological mechanism underlying cardiac syndrome X, studies suggestive that coronary micro-circular abnormalities and endothelial dysfunction play a role in the aetiology of the disease. Atherosclerosis and endothelial vasomotor dysfunction have been suggested as possible contributing factors.⁶⁻⁸

There are limited data in literature to compare the MPV in cardiac syndrome X. This study was designed to compare MPVs of patients with cardiac syndrome X, patient with CAD and of normal controls.

METHODS

Nine hundred and forty four patients who had undergone coronary angiography between May 2014 and April 2016 in Rajarajeshwari Medical College and Hospital, Bangalore, were retrospectively examined. Of these, 118 patients were enrolled in the study and were divided into three groups.

The cardiac syndrome X-group consisted of 40 subjects (18 men and 22 women with mean age group 45+4.2 years). The diagnosis of cardiac syndrome X was based on the presence of typical exercise-induced angina pectoris that was associated with transient ischaemic ST segment depression (>1 mm) during the treadmill exercise testing with normal coronary angiogram in the absence of coronary artery spasm as determined by hyperventilation manoeuvre.

The CAD group consisted of 33 subjects (18 men and 15 women with mean age of 46+4.8 years) with CAD, which was defined as >50% stenosis in a minimum of one coronary artery.

The control group consisted of 45 age and sex matched individuals (23 men and 22 women with mean age of 45+4.5 years) who presented with chest pain, normal coronaries and no ischaemia during treadmill exercise testing.

Written informed consent was obtained from all of the participants prior to enrolment. The Institutional Ethics Committee approved the study protocol.

All the subjects were evaluated with a detailed medical history, physical examination and biochemical analysis which included 12-hour fasting lipid profile (includes low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride). All of the subjects were questioned regarding cardiovascular drug use, smoking and alcohol consumption. All the subjects underwent transthoracic echocardiography for structural heart disease.

The exclusion criteria included the following: refusal to participate in the study and presence of hypertension, diabetes, left ventricular dysfunction (left ventricular ejection fraction <50% or hypertrophy, unstable ischaemic condition (unstable angina pectoris and myocardial infarction), valvular heart disease, congenital heart disease, any observed abnormality in thyroid function tests, renal or hepatic dysfunction (Creatinine >1.2 mg/dL, aspartate aminotransferase and alanine transaminase levels that were higher than double the upper limits of normal, respectively), primary haematological disorder, inflammatory diseases, any

infection within three months and any medication that could affect the MPV.

Cardiac Catheterization

The coronary angiograms were performed with a radial approach using the TIG catheter with the use of heparin 2500 units, 100 microgram of Nitroglycerin and 100 microgram of diltiazem. Following the appropriate patient preparation, the entire patient in the study population underwent elective coronary artery arteriography using Siemens Catheterization lab. Two experienced cardiologists who were blinded to the study subject's group assignment evaluated all of the angiograms. The coronary angiograms were judged with regards to a smooth appearance, luminal wall irregularities, Epicardial local or diffuse caliber reduction or stenosis. The coronary arteries were classified as normal on the basis of visual assessment of the absence of any luminal irregularities. To exclude the possibility of coronary artery vasospasm, the patient who exhibited normal coronary anatomy underwent a hyperventilation test during the coronary arteriography. The hyperventilation test was performed by asking the patient to breathe rapidly and deeply for 5 minutes.

Biochemical Measurement

The blood samples were withdrawn without stasis on the morning of the day prior to the coronary angiography and following a fasting period of 12 hours. The glucose, creatinine, and lipid profiles were determined using standard methods. For all the groups, we measured the MPV from the blood samples that were obtained following the venepuncture. The blood was collected in tripotassium EDTA tubes. We analysed the blood samples of all of the groups using an automatic blood counter after two hours of venepuncture. This period of time was waited to allow for the stabilization of platelet shape changes.

Statistical Analyses

The continuous variables are reported as the mean±standard deviation, whereas the categorical variables were defined as percentages. The Statistical Package for the Social Sciences (SPSS) statistical software package version 15 for windows was used for the statistical analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

The primary characteristics of the study population are given in Table 1. There was no statistical significance between the three groups with respect to age, sex, smoking or alcohol consumption ($p=NS$). There was a female preponderance in cardiac syndrome X group, but not statistically significant. The body mass indexes, lipid profiles and fasting glucose levels did not differ between the three groups. Likewise, the laboratory characteristics of all of the groups were not significantly different. There were no statistically significant differences in the MPV measurements between the cardiac syndrome X group and CAD groups. (Mean MPV 12.2±1.4 fL vs. 13.8±2.1 fL, $p=NS$). The MPV was significantly higher in both Cardiac syndrome X (mean=12.2±1.4 fL) and CAD group (mean=13.8±2.1 fL) compared with the control groups (mean=7.9±1.1 fL) ($p < 0.01$).

	Control Group (n= 45)	Cardiac Syndrome X Group (n=40)	CAD Group (n=33)	p Valve
Age, yrs.	45.3± 4.5	45.3±5.1	46.2± 4.8	NS
Gender (M), n (%)	23 (51)	18(45)	18(54)	NS, p = 0.08
Active smoker, % (n)	24.4 (11)	25 (10)	24(8)	NS
Alcohol consumption, % (n)	11(5)	10(4)	9(3)	NS
BMI (kg/m ²)	26.8± 4.1	27.9±5.6	26.1± 4.1	NS, p= 0.11
Fasting blood glucose (mg/dL)	99± 9	104 ± 9	100± 11	NS
Haemoglobin (mg/dL)	12.8± 1.3	12.4±1.4	12.2± 1.3	NS
LDL cholesterol (mg/dL)	129.4± 28.3	134.6± 24.3	135.4± 33.3	NS
HDL cholesterol (mg/dL)	35.4± 8.9	34.5±7.8	34.2± 6.7	NS
Triglycerides (mg/dL)	168.9± 57.2	170.4 ± 60.2	169.2± 69.3	NS
Creatinine (mg/dL)	0.98 ± 0.14	1.07±0.22	1.02± 0.18	NS
Platelet count (L/cumm)	1.66± 0.22	1.64 ±0.44	1.71± 0.21	NS
Mean platelet volume (fL)	7.9±1.1	12.2±1.4	13.8± 2.1	P = 0.01

Table 1: The Baseline Clinical and Biochemical Characteristics of the Study Groups

DISCUSSION

Patients with Cardiac Syndrome X have been stated to have multiple pathophysiological abnormalities.⁹ Generalized endothelial dysfunction and inflammation were reported as the most convincing evidence of cardiac syndrome X.^{10,11} Also in the patient with cardiac syndrome X; inflammation was thought to be related to endothelial dysfunction. Elevated levels of inflammatory molecules were previously reported as markers of atherosclerotic disease activity and as an indication of increased risk from the progression of atherosclerosis.¹² Moreover, inpatients with either coronary artery disease or Cardiac Syndrome X, creative protein was reported to be associated with impaired endothelial function. CRP levels was found to be correlated with the activity of the disease. In a similar vein, elevated Red Cell Distribution Width (RDW) levels were found to be independently associated with presence of Cardiac Syndrome X, and in the same study RDW and CRP levels were reported to correlate positively.¹³ In another study, the presence of endothelial dysfunction and sub-angiographic atheroma was revealed in patients with Cardiac Syndrome X.¹⁴ Furthermore, some intravascular ultrasonographic studies with Cardiac Syndrome X patients discovered presence of abnormal coronary arteries with atheromatous plaques and intimal thickening.^{14,15} Additionally, magnetic resonance imaging revealed abnormal sub-endocardial perfusion in patients with Cardiac Syndrome X.¹⁶ For all these reasons, it could be considered that the aetiopathogenesis of coronary artery disease and Cardiac Syndrome X are similar.

Platelets play an important role in the pathogenesis, morbidity and mortality of acute coronary syndromes.¹⁷ Increased platelet activation and aggregation were reported to be closely associated with cardiovascular complications.¹⁸ The average size of platelets is described as mean platelet volume. Larger platelets have been found to be biologically more active and their pro-thrombotic properties are more powerful.

In another study, the relationship between MPV and angiographic severity of coronary artery disease was investigated and a positive correlation between them was found.¹⁸ Cay et al documented elevated MPV in patients with acute coronary syndrome and CSX.¹⁹ Similar to our study, Demirkol et al²⁰ showed that the MVP values were significantly higher in the Cardiac Syndrome X and coronary artery disease groups than those of the control group.

Platelet function can be affected by several factors such as platelet count, size, density, platelet age, a higher granule count and adhesion receptor expression as well as higher mean platelet volume. MPV appears to correlate more closely with platelet volume than does platelet count alone.²¹ Even though various methods like optical aggregometry, platelet function analysis using PFA-100 system, platelet reactivity tests, platelet aggregate ratio measurements, flow cytometry and thromboxane B2 generation tests²² are there to analyse the platelet activation, but they are of limited use due to complex pre-analytical factors, reduced specificity and poor reproducibility. MPV is a simpler marker that does not require advanced or expensive technology. MPV may reflect platelet production and stimulation; therefore, elevated MPV value may indicate cardiovascular disease. Increased MPV may be due to the body's use of small platelets during acute ischaemia.²³ Thus, MPV has become a prognostic factor in coronary heart disease and may eventually be accepted as a parameter of platelet activity.²⁴ In addition, several reports have demonstrated that there is a close relationship between MPV and cardiovascular risk factors including impaired fasting glucose levels, diabetes mellitus, hypertension, hypercholesterolemia, obesity and metabolic syndrome.²⁵⁻²⁷ It has been reported that elevated MPVs are associated with cardiovascular diseases.²⁸ It is also known that increased platelet activation and aggregation are closely related to cardiovascular complications.²⁴

The primary limitation of our study was the comparatively small size of the study population. Another limitation was the possibility of underlying coronary artery spasm in patients with Cardiac Syndrome X, which was excluded using a hyperventilation test, although the ergonovine test would have been the ideal test in this contest. Also, coronary flow reserve measurement using Doppler wire and intravascular ultrasound are two invasive methods that could be used in the diagnosis of microvascular disease and exclusion of atheromatous plaques on the coronary vessel wall, respectively. Positron emission tomography might be used for detection of abnormalities in the coronary vasomotor functions caused by microvascular disease and to measure the coronary flow reserve. Moreover, perfusion abnormalities caused by coronary microvascular disease could be reliably detected by contrast stress echocardiography and cardiac magnetic resonance, which are non-invasive assessments.

None of these tests were performed in our study subjects, who were assessed retrospectively in this study.

CONCLUSION

MPV was significantly higher in patients with either Cardiac Syndrome X or Coronary Artery Disease relative to the control, but with no statistically significant differences were observed between the Cardiac Syndrome X and the CAD groups. Elevated MPVs may participate in the pathogenesis of Cardiac Syndrome X. Prospective, placebo-controlled studies with large sample sizes that use multivariable survival analyses and long-term follow-up periods are required for the clinical evaluation of the prognostic value of increased MPV in patients with Cardiac Syndrome X.

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