Microvascular Angina. The Possible Role of Inflammation, Uric Acid, and Endothelial Dysfunction

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SUMMARY

Microvascular angina is a condition characterized by angina-like chest pain and normal coronary angiography. Endothelial dysfunction and systemic inflammation with elevated serum high-sensitive C-reactive protein (hsCRP) levels play a role in its pathogenesis. This study aimed to explore the possible relation between CRP, brachial flow-mediated dilatation (FMD), and microvascular angina.

We included 21 patients with attacks of chest pain diagnosed as microvascular angina (study group) and 10 normal asymptomatic subjects (control group). Patients and controls were thoroughly examined clinically and by echocardiography, electrocardiography, and brachial FMD (using external brachial ultrasonography). Serum hsCRP and uric acid levels were assessed in all subjects.

A significantly higher mean hsCRP level was found in the study group compared to controls (11.5 ± 3.8 versus 3.34 ± 1.5 mg/L; $P < 0.001$). FMD of the brachial artery showed significant impairment in patients with microvascular angina compared to controls (0.16 ± 0.06 versus 0.76 ± 0.09 mm; $P < 0.001$). There were significantly higher total cholesterol (196.1 ± 44.4 versus 159.8 ± 14.5 mg/dL; $P = 0.018$) and triglyceride levels (185.0 ± 103.2 versus 113.0 ± 17.6 mg/dL; $P = 0.038$) in the patients compared to controls; but there was a statistically insignificant difference in mean serum uric acid levels between these two groups. There were no significant correlations between the brachial FMD and any of the clinical variables studied (apart from ankle/brachial index).

Microvascular angina may have an inflammatory element (reflected as a higher serum hsCRP level), together with a contribution by endothelial dysfunction (reflected as impaired brachial artery FMD); while serum uric acid is possibly not associated with microvascular angina. (Int Heart J 2009; 50: 407-419)

Key words: Syndrome X, C-reactive protein, Flow-mediated dilatation

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FOR over a century, angina pectoris has been considered the clinical hallmark of ischemic heart disease. However, widespread introduction of selective coronary angiography demonstrated that a significant proportion (up to 20-30%) of patients presenting with classic chest discomfort suggestive of angina had angiographically normal epicardial coronary arteries.^{1,2)} With increasing evidence of the new disorder in 1973, Kemp³⁾ introduced the term “syndrome X” to describe for the first time a group of patients with exercise-induced angina and normal coronary angiograms. Early studies investigating this phenomenon demonstrated that despite normal coronary vessels, the affected patients had electrocardiographic (ECG) as well as metabolic evidence of myocardial ischemia.⁴⁻⁶⁾

Systemic inflammation may also play an important role in the pathogenesis of vascular dysfunction in syndrome X.⁷⁾ C-reactive protein (CRP), a sensitive marker of inflammation, is known to be associated with vascular dysfunction.⁸⁾ In addition, substantial evidence suggests a significant association between enhanced serum uric acid levels and cardiovascular morbidity and mortality, despite its known antioxidant activity.⁹⁾

Endothelial dysfunction is one of the initial pathological processes of atherosclerosis and has been associated with increased cardiovascular risk. Brachial flow-mediated dilation (FMD) is a validated noninvasive physiological measure widely used as a research tool to quantify endothelial function. Brachial FMD has been shown to be an independent predictor of cardiovascular outcomes.¹⁰⁾

The aim of the current study was to test the possible association between the levels of a representative inflammatory marker (CRP), serum uric acid, and endothelial dysfunction (represented by brachial FMD) and microvascular angina on the other hand.

METHODS

Study design and participants: The study group comprised 21 patients (10 males) who underwent diagnostic studies to investigate their anginal symptoms. All patients had normal selective coronary angiography reviewed independently by two cardiologists, and objective evidence (conventional and exercise ECG) of myocardial ischemia. Only the patients followed-up for at least 1 year were included.

Ten subjects (5 males and 5 females) without chest pain and negative ECG exercise test were considered as the control group. These controls had normal resting ECG, and were recruited from an internal database of Mansoura University Hospital. Initially, 17 subjects were invited to participate in our study by a letter (another was sent in case of no response) and telephone calls (whenever

Figure 1. Exercise ECG showing horizontal ST-segment depression in leads V3-V6 immediately during recovery (microvascular angina group, patient No. 2).

possible). Agreement to participate was received from 13 subjects, 3 of whom later withdrew. Thus, 10 subjects remained and were included in this study.

Both patients and controls were free of diabetes and hypertension, and all

of them were currently nonsmokers (only 3 male patients and 2 male controls were ex-smokers, who declared complete cessation of smoking for at least 2 years). All patients and controls denied previous or current alcohol intake, and were not under any medical treatment.

Clinical evaluation included complete history and physical examination, chest X-ray, resting and maximal exercise ECG, fasting serum lipid profile, and lipoprotein electrophoretic pattern. Fasting and 2-hour postprandial blood glucose tests were performed in all patients.

All the patients included in this study had episodic chest discomfort consistent with anginal syndrome. These complaints were considered typical of angina pectoris when they were felt to conform to the board criteria outlined by Hurst and Logue¹¹⁾ by at least two physicians. The chest pain syndrome was considered atypical angina pectoris when some inconsistent features were present with respect to location, duration, or provocation by effort or stress.

Exercise ECG: All patients underwent a multistage treadmill exercise test with the standard Bruce protocol. Criteria for interrupting the test were: severe chest pain, diagnostic ST-segment shift ≥ 2 mm, extreme dyspnea or fatigue, systolic blood pressure > 240 mmHg, diastolic blood pressure > 120 mmHg, or reaching the maximal age-predicted heart rate. ECG was diagnostic for ischemia when there was ≥ 1 mm flat or downsloping ST-segment depression 0.08 seconds after the J-point (Figure 1).

Endothelial measurements: The subjects were kept in the supine position in a quiet, dark, and air-conditioned room (with a constant temperature of 23-26°C throughout the study). After 20 minutes of rest, basal brachial artery diameter was measured. Endothelium-dependent and endothelium-independent vasodilations were examined in the brachial artery using external ultrasound.

The right brachial artery was scanned in the longitudinal section 3 - 5 cm above the antecubital fossa using a high-resolution external ultrasound (Vivid 3 model) with a 10-MHz linear-array transducer. Forearm blood flow was altered by inflating a blood pressure tourniquet placed around the forearm. The cuff was inflated to 20 mmHg higher than the systolic blood pressure for 5 minutes. Endothelium-dependent FMD was assessed as the percent change in the arterial diameter in response to reactive hyperemia associated with 5 minutes of ischemia (Figures 2 - 4).

The diameter change induced by FMD was expressed as the percent change relative to that at the initial scan (FMD %) according to the following equation¹⁰⁾

$$\text{FMD \%} = \frac{\text{Maximum diameter} - \text{Baseline diameter}}{\text{Baseline diameter}} \times 100$$

Echocardiographic studies: Transthoracic Doppler-echocardiographic recordings

were obtained using a real-time phased array sector scanner (Vivid 3 model) with an integrated color Doppler system and a transducer containing crystals for

Figure 2. Longitudinal section of brachial artery at baseline before cuff inflation (microvascular angina group, patient No. 4).

Figure 3. Longitudinal section of brachial artery after cuff inflation (microvascular angina group, patient No. 4).

Figure 4. Cross section of brachial artery after cuff inflation (microvascular angina group, patient No. 4).

imaging at 2.5 - 4.0 MHz with second harmonic capabilities.

For continuous and pulsed wave Doppler recordings (including tissue Doppler imaging), the transducer emitted at 1.9 MHz; conventional transthoracic Doppler echocardiography was performed. The subjects were examined in the supine and left lateral position.

All patients and controls underwent conventional, M-mode, and two-dimensional echocardiography from the left parasternal and apical windows. M-mode measurements of the left ventricle (LV) were obtained during end systole and end diastole. Both LV and left atrial cavitory diameters were measured according to the leading edge method. LV cavitory dimensions for the calculation of LV ejection fraction were obtained from biplane projection. LV mass (LVM) was calculated from M-mode records taken on parasternal long-axis images according to the method recommended by the American Society of Echocardiography [$\text{LV mass (g)} = 0.8 \times (1.04 [\text{LVDd} + \text{IVST} + \text{PWT}]^3 - \text{LVDd}^3) + 0.6$] and then was indexed to body surface area (m^2); where LVDd = left ventricular diastolic dimension (mm), IVST = interventricular septum thickness (mm), and PWT = posterior wall thickness (mm).

Laboratory measurements:

Lipid profile. Assessment of serum total cholesterol (TC), triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-C) levels was performed using enzymatic colorimetric methods (Human, Wiesbaden, Germany), and

serum low-density lipoprotein-cholesterol (LDL-C) was estimated using Friedewald's formula.

Serum C-reactive protein. Serum level of hsCRP (Diasyslab Inc., Webster, USA) was measured by an ELISA technique according to the manufacturer's protocol.

Serum uric acid. Serum uric acid levels were determined with an enzymatic colorimetric method on an Aeroset Clinical Chemistry Analyzer (Abbott Lab., Abbott Park, Illinois, USA).

Statistical analyses: Data analyses were performed with SPSS for Windows version 13 (SPSS Inc., Chicago, IL). Results are expressed as the mean $\pm$ standard deviation of the mean for continuous data. Comparison of the means of continuous variables across a grouping variable with 2 levels was performed using

Table I. Baseline Characteristics and Comparisons of the Patients With Microvascular Angina (Study Group) and Normal Asymptomatic Subjects (Control Group) Included in This Study

Variable	Study group (n = 21)	Control group (n = 10)	P (non-adjusted)	P (adjusted) [§]
Demographic data				
Age (years)	49.7 $\pm$ 7.3	46.8 $\pm$ 6.8	0.272	-
Male gender	10 (48%)	5 (50%)	0.901	-
Anthropometric/medical measurements				
Body mass index (kg/m ²)	31.6 $\pm$ 2.7	31.1 $\pm$ 4.9	0.715	-
Body weight (kg)	85.7 $\pm$ 17.2	83.2 $\pm$ 16.1	0.703	-
Height (cm)	163.9 $\pm$ 13.6	164.2 $\pm$ 10.5	0.951	0.945
Heart rate (beat/min)	82.4 $\pm$ 8.6	78.9 $\pm$ 10.8	0.337	0.395
Systolic blood pressure (mmHg)	115.5 $\pm$ 14.9	112.0 $\pm$ 10.9	0.514	0.608
Diastolic blood pressure (mmHg)	73.5 $\pm$ 10.7	72.4 $\pm$ 8.8	0.779	0.805
Ankle/brachial index	1.14 $\pm$ 0.11	1.19 $\pm$ 0.09	0.222	0.351
Laboratory measurements				
hs C-reactive protein (mg/L)	11.5 $\pm$ 3.8	3.3 $\pm$ 1.5	< 0.001**	< 0.001**
Uric acid (mg/dL)	4.75 $\pm$ 0.97	4.58 $\pm$ 0.82	0.641	0.687
Total cholesterol (mg/dL)	196.1 $\pm$ 44.4	159.8 $\pm$ 14.9	0.018*	0.024*
LDL-cholesterol (mg/dL)	113.9 $\pm$ 38.9	93.4 $\pm$ 16.7	0.122	0.111
HDL-cholesterol (mg/dL)	42.4 $\pm$ 5.6	46.6 $\pm$ 3.3	0.036*	0.041*
Triglycerides (mg/dL)	185.0 $\pm$ 103.2	113.0 $\pm$ 17.6	0.038*	0.036*
Echocardiographic data				
Ejection fraction (%)	66.2 $\pm$ 2.4	66.4 $\pm$ 1.7	0.764	0.801
Left ventricular mass index (g/m ²)	81.2 $\pm$ 20.5	76.5 $\pm$ 18.7	0.547	0.501
Endothelial measurements				
Brachial basal diameter (CS) (mm)	4.84 $\pm$ 0.74	4.74 $\pm$ 0.99	0.748	0.733
Brachial basal diameter (LS) (mm)	4.67 $\pm$ 0.82	4.43 $\pm$ 1.04	0.488	0.409
Brachial FMD (LS) difference	0.12 $\pm$ 0.08	0.82 $\pm$ 0.13	< 0.001**	< 0.001**
Percent change FMD (LS)	4.78 $\pm$ 0.67	5.24 $\pm$ 0.85	0.114	0.143
Brachial FMD (CS) difference	0.16 $\pm$ 0.06	0.76 $\pm$ 0.09	< 0.001**	< 0.001**
Percent change of FMD (CS)	5.00 $\pm$ 0.70	5.53 $\pm$ 0.95	0.088	0.102

[§] Adjustment for age, gender, and body mass index. Data are expressed as mean $\pm$ standard deviation of mean. CS indicates cross-section; FMD, flow-mediated dilatation; HDL, high-density lipoprotein; hs, high-sensitive; LDL, low-density lipoprotein; and LS, longitudinal section.

* = $P < 0.05$, ** = $P < 0.01$.

Student's *t*-test. Proportions were compared by using the χ^2 test or Fisher's exact test when appropriate. A 2-sided significance level of 0.05 was used for all analyses.

RESULTS

The baseline characteristics and comparisons of the patients with microvascular angina (study group) and normal asymptomatic subjects (control group) included in this study are summarized in Table I.

Figure 5. Bar graph showing the distribution of mean serum hsCRP and uric acid levels in patients with microvascular angina and normal control subjects.

Table II. Partial Correlations[§] of Changes in FMD % Values With the Other Variables Studied

Variable	Brachial artery cross section difference		Brachial artery longitudinal section difference	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Uric acid	- 0.361	0.070	- 0.131	0.525
hs C-reactive protein	0.213	0.296	0.163	0.426
Ankle/brachial index	- 0.194	0.343	- 0.427	0.030 [*]
Total cholesterol	0.045	0.828	0.078	0.704
HDL-cholesterol	0.031	0.881	0.124	0.545
LDL-cholesterol	0.049	0.812	0.058	0.779
Triglycerides	- 0.074	0.719	- 0.187	0.360

[§]Adjustment for age, gender, body mass index, and clinical presentation (patient or control group).

Abbreviations as in Table I.

Table III. Partial Correlations[§] of Serum hsCRP and Uric Acid Levels With the Other Variables Studied

Variable	Serum uric acid		Serum hsCRP	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Uric acid	-	-	- 0.044	0.831
hs C-reactive protein	- 0.044	0.831	-	-
Ankle/brachial index	0.048	0.815	0.091	0.660
Total cholesterol	0.067	0.744	0.656	< 0.001**
HDL-cholesterol	0.185	0.364	- 0.421	0.032*
LDL-cholesterol	0.178	0.383	0.642	< 0.001**
Triglycerides	0.484	0.012*	- 0.113	0.582

[§] Adjustment for age, gender, body mass index, and clinical presentation (patient or control group).
Abbreviations as in Table I.

This study comprised 21 patients with chest pain and positive exercise ECG test typical of ischemia. All patients had normal coronary angiography. They were 10 males and 11 females with a mean age of 49.7 ± 7.3 years.

Serum hsCRP levels were significantly higher in the study group compared to controls ($P < 0.001$). This difference remained statistically significant even after multivariate adjustment for the possible confounders as shown in Table I.

Brachial artery FMD was significantly impaired in the study group compared to the normal subjects. Serum TC and TG levels were significantly higher in the study group than in normal controls; while the reverse was found regarding serum HDL-C, which was significantly higher in the control group compared to the patients. No statistically significant difference was observed between patients and controls regarding the mean serum uric acid level (Figure 5).

Correlations of the changes in brachial artery: Correlations of the brachial artery cross and longitudinal section differences (before and after cuff inflation) with the clinical and laboratory variables in the study population did not reach statistical significance. The only variable which showed a significant correlation with the brachial artery longitudinal section difference was the ankle/brachial index (Table II).

Correlations of serum uric acid levels: Correlations of serum uric acid values with the clinical and laboratory parameters of the study population did not reach statistical significance. Only serum TG values showed a significant correlation with serum uric acid levels (Table III).

Correlations of serum hsCRP levels: Serum hsCRP levels significantly correlated positively with TC and LDL-C, and negatively with HDL-C values. Correlations with the other clinical and laboratory variables were not significant (Table III).

DISCUSSION

Cardiac syndrome X is a clinical entity characterized by angina-like chest discomfort (often prolonged), normal coronary arteries (assessed by arteriography), noninducible coronary vasospasm with ergonovine provocation, and ST-segment depression on treadmill exercise testing.¹²⁾ Since its first description, it was suggested that angina is caused by myocardial ischemia determined by a dysfunction of small resistance coronary vessels not visible at coronary angiography, a condition defined as “microvascular angina”.¹³⁾ The causes of microvascular dysfunction in cardiac syndrome X are likely to be multiple. A frequently reported abnormality is endothelial dysfunction (suggested by inappropriate vasoconstriction and decreased coronary flow response to acetylcholine, atrial pacing and other vasodilator stimuli), that is believed to be caused by impaired nitric oxide release and/or activity.^{4,12,14)} More recently, chronic inflammation was found to be associated with cardiac syndrome X.^{15,16)} The evidence for this was the elevated inflammatory markers associated with the disease activity and the effect of statin, a lipid-lowering as well as anti-inflammatory drug, which has significantly modified the disease process in cardiac syndrome X.¹⁷⁻¹⁹⁾

CRP is the prototypic acute phase reactant and marker of inflammation. Recent data suggest that CRP is a risk factor for cardiovascular disease and is additive to LDL-C and the 10-year Framingham risk score (FRS).²⁰⁾ In this regard, the American Heart Association and Centers for Disease Control and Prevention have recommended that an hsCRP level between 3 and 10 mg/L confers a greater risk of cardiovascular diseases in patients with a FRS of 10-20%.²¹⁾ Furthermore, serum hsCRP levels > 2.6 mg/L predicted the presence of complex coronary lesions with a sensitivity and specificity of 74% and 62%, respectively.²²⁾

It has been suggested that CRP contributes to the development of endothelial dysfunction and atherogenesis. The observed relationship between microvascular angina and CRP levels in our study, when coupled with the findings from large epidemiologic trials suggesting that high CRP levels constitute a risk factor for cardiovascular events both in apparently healthy individuals²³⁾ and in patients with angina pectoris,^{24,25)} indicates that inflammation may play a significant role in microvascular angina.

Higher serum CRP levels have been associated with blunted systemic endothelial vasodilator function.²⁶⁾ Two indices of systemic inflammation, CRP and interleukin-1 receptor antagonist, have been reported to increase in patients with cardiac syndrome X compared with healthy controls, suggesting that a low-grade inflammation may play a pathogenetic role.¹⁵⁾ Increased levels of CRP were found in patients with cardiac syndrome X; and evidence of a more active

disease was indicated by a more severe angina, more frequent episodes of ST-segment depression during Holter monitoring, and earlier and more evident ischemic ST-segment changes during exercise stress testing.

Elevated serum uric acid concentrations seem to be a graded marker of risk for the development of coronary or cerebrovascular diseases and stroke.²⁷⁻²⁹⁾ Previous studies investigating the relationship between uric acid and coronary artery disease showed conflicting results, and there is still an intense debate whether an elevated serum uric acid level has a causal relationship with cardiovascular diseases, and whether a reduction of its level would be an element in the preventive strategy of these diseases. The simple concept that “serum uric acid levels in patients with cardiovascular diseases may reflect a compensatory mechanism to counter oxidative stress” is intriguing. However, this cannot explain why elevated serum uric acid levels in patients with cardiovascular diseases are generally associated with worse outcomes.³⁰⁾

Several possible pathologic mechanisms linking serum uric acid to cardiovascular disease have been proposed, including deleterious effects on endothelial function, oxidative metabolism, and platelet adhesiveness and aggregation. In addition, serum uric acid should be considered as one of the multiple injurious stimuli to the arterial vessel wall and capillaries, which may contribute to endothelial dysfunction and arterial-capillary vessel wall remodeling through oxidative stress.^{28,31)} Furthermore, several studies have suggested that serum uric acid levels could be as predictive as hsCRP because it is a sensitive marker for underlying inflammation and remodeling within the arterial vessel wall and the myocardium.^{32,33)} In our study, we found a nonsignificant difference in the serum uric acid levels between the patient and control groups. Moreover, there were no significant correlations between serum uric acid levels and the other clinical and laboratory variables (apart from serum TG) in the population studied.

The majority of earlier studies on the association between brachial FMD and incident cardiovascular events were conducted in relatively young subjects with established cardiovascular diseases. Some of these studies showed an association between brachial FMD and incident cardiovascular events,³⁴⁻³⁶⁾ but other studies did not show any association.³⁷⁾ The association between brachial FMD and incident cardiovascular events was studied in an asymptomatic population-based multiethnic cohort composed of 842 subjects.³⁸⁾ Although an association was found between brachial FMD and incident cardiovascular events, the predictive value of FMD was not independent of the traditional cardiovascular risk factors.³⁸⁾ In our study, there was a significantly lower brachial artery FMD in the patients with microvascular angina compared to normal controls ($P < 0.001$). This finding is in agreement with the results obtained from the Cardiovascular Health Study,¹⁰⁾ and could be translated as evidence of a possible pathogenetic

role of endothelial dysfunction in microvascular angina.

Conclusions: From our results, we may conclude that microvascular angina has a possible inflammatory element (reflected as a higher serum hsCRP level), together with a potential contribution by endothelial dysfunction (reflected as impaired brachial artery FMD); while serum uric acid, which is considered a novel inflammatory marker, is possibly not associated with microvascular angina.

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