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Increased Arterial Stiffness in Patients with Cardiac Syndrome X

- Pulse Wave Velocity in Cardiac Syndrome X -

Young-Soo Lee, M.D., Kee-Sik Kim, M.D., Chang-Wook Nam, M.D. and Yoon-Nyun Kim, M.D.
Department of Internal Medicine, Keimyung University, College of Medicine, Daegu, Korea

ABSTRACT

Background and Objectives : Up to 10% of coronary angiograms performed for the assessment of patients with chest pain show a normal coronary anatomy. Arterial dysfunction has been reported in patients with cardiac syndrome X (CSX). The Pulse Wave Velocity (PWV) has been shown to be an indicator of arterial stiffness. The aim of this study was to evaluate the atherosclerotic risk factors and arterial stiffness by measuring the pulse wave velocity in patients with CSX. **Subjects and Methods :** Sixty patients, with typical chest pain and a normal coronary anatomy, were enrolled, and divided into 2 groups; the CSX group, consisting of 34 patients (male: 14, mean age 57.1±11.5 years) with a positive stress tests, and the control group, which contained 26 patients (male: 7, mean age: 55.4±10.9 years), who were diagnosed with gastro-esophageal disorders. Arterial stiffness was assessed by measuring the carotid-radial PWV. The cardiovascular risk factors, including body mass index, lipid profile, left ventricular mass, pulse pressure, plasma homocysteine and C-reactive protein, were also measured. **Results :** The PWV was significantly higher in patients with CSX than in the controls (10.28±1.02 vs. 8.62±1.18 m/s, $p<0.05$). However, there was no difference in the other atherosclerotic risk factors between the groups. The cutoff value for PWV was 9.85 m/s, with sensitivity and specificity of 65 and 88%, respectively. **Conclusion :** In patients with CSX, the arterial stiffness was increased compared to the controls, but no increase the cardiovascular risk factors were observed. PWV assessment might be a helpful tool in identifying CSX patients with chest pain of a noncardiac origin. **(Korean Circulation J 2005;35:424-428)**

KEY WORDS : Pulse ; Atherosclerosis ; Cardiac Syndrome X.

Introduction

Approximately 10% of all coronary arteriograms perormed for the assessment of patients with chest pain show a normal coronary anatomy.[1-3] In 1973, Kemp et al.[4] defined syndrome X as a condition characterized by typical chest pain and ECG changes suggestive of myocardial ischemia, despite the presence of angiographically normal coronary arteries. Coronary endothelial dysfunction, leading to microvascular angina[5][6] and impaired coronary flow reserve,[7][8] have been proposed as the pathogenetic mechanism for cardiac syndrome X (CSX). The abnormal findings of myocardial perfusion in CSX patients can be explained by an impaired vasoation capacity of the coronary arteries.[9] A common finding for the majority of patients with CSX is endothelial dysfunction of the coronary arteries,[10] and microvascular angina is also part of the early stage of coronary artery atherosclerosis, but this escapes angiographic recognition.[11] The morphological abnormalities seen in arteriosclerosis are prone to elevate the stiffness of vessel wall.[12] In the Rotterdam study, Popele et al.[13] reported that arterial stiffness, as measured by the pulse wave velocity, was strongly associated with atherosclerosis at various sites in the vascular tree. The aim of this study was to evaluate the atherosclerotic risk factors and arterial stiffness by measuring the pulse wave velocity in patients with CSX.

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Correspondence : Kee-Sik Kim, M.D., Department of Internal Medicine, Keimyung University, College of Medicine, 194 Dongsan-dong, Jung-gu, Daegu 700-712, Korea
Tel: 82-53-250-7379, Fax: 82-53-250-7034
E-mail: kks7379@dsmc.or.kr

Subjects and Methods

Patients population

Sixty patients, who had typical chest pain and a normal coronary anatomy, were enrolled, and divided into 2 groups; the CSX group, consisting of 34 patients (males: 14, mean age: 57.1±11.5 years) with a positive stress ECG or positive myocardial perfusion scintigraphy

test, and the control group, consisting of 26 patients (males: 7, mean age: 55.4±10.9 years), who were diagnosed with gastro-esophageal disorders, such as gastric and duodenal ulcer, gastroesophageal reflux disease and esophageal motility disorder. The diagnosis of CSX was based on the presence of typical angina pectoris, transient >1 mm ST-segment depression during exercise stress testing or a transient perfusion defect, as noted during myocardial perfusion scintigraphy; all subjects had angiographically normal coronary arteries, with the absence of coronary artery spasms and left ventricular hypertrophy. The exclusion criteria were a previous myocardial infarction, previous percutaneous coronary intervention, valvular heart disease, cardiomyopathy, sinus node dysfunction, atrial fibrillation, conduction disturbance, known peripheral arterial disorders, diabetes mellitus and impaired renal and/or liver function. All the patients were receiving antianginal or anti-hypertensive treatment prior to their entry onto the study, which were withdrawn for at least 48 hours before the study commenced. All patients gave their written informed consent before entering the study.

Study protocol

Coronary angiography was performed for all patients using the standard Judkins method, which were subsequently analyzed by two experienced investigators, working independently. Only those angiograms with visually smooth contours, with no wall irregularities, were accepted as normal. During coronary arteriography, to exclude the possibility of coronary artery vasospasm, all patients underwent a hyperventilation test, which was performed by asking the patients to breathe quickly and deeply for 5 minutes.

An exercise test (the Bruce protocol) was adjudged positive if there was at least 0.1 mV of horizontal ST segment depression or elevation on at least two of the leads. The ECG exercise test was aborted if the heart rate reached a submaximal value, if the patient complained of chest pain, complex forms of cardiac arrhythmias were observed or if the criteria for a positive ECG test were reached.

Echocardiographic assessment was performed in all patients, according to the standards of the American Society of Echocardiography, using measurements of the left ventricle mass, the left atrium volume and the left ventricular ejection fraction.

Biochemical tests

After night fasting, baseline venous blood samples were obtained from the large antecubital vein in all patients and controls. The serum lipid levels were measured using routine methods. C-reactive protein measurements were performed using the Nephelometer (Dade Behring Inc, Newark, DE, U.S.A.) method. Plasma homocysteine measurements were assessed by a fluorescence polarization immunoassay using an IMx Analyzer (ABBOTT Laboratories, Axis-Shield, Oslo, Norway). The concentration of pro-brain natriuretic peptide (BNP) was measured using Electro Chemiluminescence (ECL) technology (Roche Diagnostics, Bazel, Swiss).

Analysis of pulse waveform

After the blood pressure measurement, the PWV measurement was performed in a controlled environment, using an automatic device, the Sphygmocor apparatus (ATCORMedical, Sydney, Australia), which uses the principle of pressure wave reflection from the periphery, and its summation with the forward-going wave. Normally, the reflected wave arrives in the central arteries after closure of the aortic valve, which does not influence the central systolic pressure. However, in the presence of increased arterial stiffness, the increased pulse wave velocity of stiffened arteries causes an earlier wave reflection, which reaches the heart during early systole. In brief, the common carotid artery and radial artery pressure waveforms were non-invasively recorded using a pressure-sensitive transducer. The pressure waveforms were digitalized at a sample acquisition frequency of 500 Hz. The 2 pressure waveforms were then stored in a memory buffer. A preprocessing system automatically analyzed the gain in each waveform, with the subsequent adjusted for the equality of the 2 signals. When the operator observed a pulse waveform of sufficient quality on the computer screen, digitization was suspended, and the calculation of the time delay between the 2 pressure upstrokes then initiated. The distance traveled by the pulse wave over the body surface was measured as the distance between the 2 recording sites (D), while the pulse transit time (t), which was measured between the feet of the pressure waveforms recorded at these different points (foot-to-foot method), was automatically determined. The PWV was automatically calculated as PWV=D/t (Fig. 1). As previously reported,[14] the measurement was performed at 20 cardiac cycles, and when the difference of the consecutive mean data during repeated measurement was less than 0.5 m/s, the mean data was then used in the final analysis.

Statistical analysis

The SPSS 12.0 (SPSS inc., Chicago, Illinois) statistical software package was used for all the calculations. Data are presented as the means±standard deviation (SD) for continuous variables and as percentages for the categorical data. For the continuous variables, comparisons between the two groups were performed using unpaired, two-tailed t-tests. Categorical data and proportions were analyzed using Chi-square tests. The sensitivity and specificity of various cutoff points of the PWV were

examined for the diagnosis of cardiac syndrome X. The best cutoff value for the diagnosis of cardiac syndrome X was defined using receiver operating characteristic (ROC) curves, i.e., plots of sensitivity versus (1-specificity). A $p<0.05$ was regarded as statistically significant.

Results

Basic demographic and biochemical parameters

The demographic and clinical characteristics of the CSX patients and the controls are presented in Table 1. There were no significant differences between the groups with regard to age, gender, body mass index or the medication used for treatment. However, the systolic blood pressure in the CSX groups was slightly higher than that in controls. The coronary risk factors, such as smoking and hypertension history, left ventricular mass index on transthoracic echocardiography, the total cholesterol and low density lipoprotein cholesterol levels, and the plasma homocysteine and C-reactive protein levels, were no different between the two groups (Table 1, 2). The pro-BNP level of the patients with CSX was slightly higher than that in the controls, but this was not statistically significant.

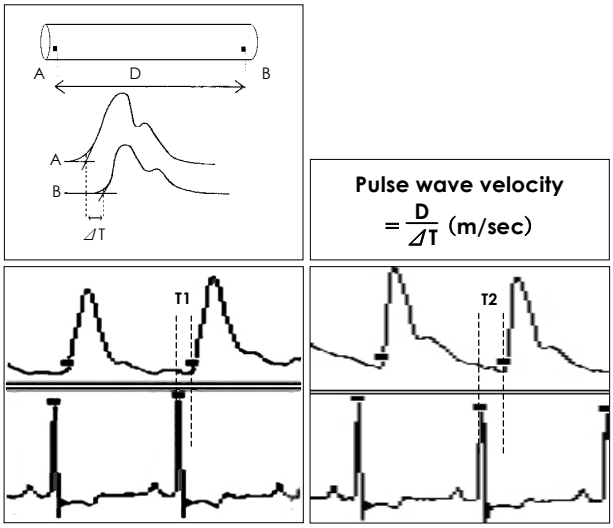

Fig. 1. Pulse wave velocity measurement. Time delay between the foot of the two waves is ⊿T=T2-T1, where T1/T2 is the time interval measured between the ECG signal and the foot of the proximal/distal wave. A: recording of the proximal site, B: recording of the distal site, D: distance traveled by the wave.

Table 1. Demographic characteristics

	Cardiac syndrome X	Controls	p
Number of patients	36	24	
Age (Yrs)	57.1±11.5	55.4±10.9	0.573
Male (%)	14 (41.2)	7 (26.9)	0.192
BMI (Kg/m^2)	24.0±2.8	23.8±3.8	0.803
Hypertension (%)	12 (35.3)	4 (15.4)	0.074
Smoker (%)	3 (8.8)	2 (7.7)	0.628
Systolic BP (mmHg)	124.8±16.1	116.7±16.7	0.063
Diastolic BP (mmHg)	71.7±10.4	68.2±12.3	0.242
Peripheral PP (mmHg)	50.8±11.2	48.5±14.9	0.503
Medication use			
Aspirin (%)	27 (79.4)	17 (65.4)	0.178
β-blockers (%)	24 (70.6)	18 (69.2)	0.566
Calcium antagonists (%)	10 (29.4)	10 (38.5)	0.322
ACE inhibitors (%)	8 (23.5)	8 (30.8)	0.368
Lipid lowering drugs (%)	7 (27.6)	6 (23.1)	0.530

Data are mean±SD. BMI: body mass index, BP: blood pressure, PP: pulse pressure, ACE: angiotensin-converting enzyme

Table 2. Biochemical and echocardiographic parameters between both groups

	Cardiac syndrome X	Controls	p
Total cholesterol (mg/dL)	195.1±33.8	177.9±35.0	0.062
HDL cholesterol (mg/dL)	46.5±9.8	48.8±13.7	0.480
Triglycerides (mg/dL)	144.2±65.4	141.8±120.4	0.924
LDL-cholesterol (mg/dL)	123.8±29.8	107.5±31.5	0.053
C-reactive protein (mg/dL)	0.18±0.54	0.17±0.32	0.948
Plasma homocysteine (umol/L)	10.8±2.9	12.1±4.6	0.280
Pro-BNP (pg/mL)	389.1±1046.1	355.7±459.8	0.890
LVEF (%)	61.9±13.1	61.7±9.8	0.955
LVMI (g/m^2)	104.3±58.5	96.3±25.6	0.533
LAVI (mL/m^2)	31.1±9.5	35.4±8.8	0.084

Data are mean±SD. HDL/LDL: high/low density lipoprotein. BNP: brain natriuretic peptide, LVEF: left ventricular ejection fraction, LVMI: LV mass index, LAVI: left atrium volume index

Table 3. Analysis of aortic pulse waveform between both groups

	Cardiac syndrome X	Controls	p
Central SBP (mmHg)	113.7±16.5	106.7±17.6	0.119
Central DBP (mmHg)	72.3±10.5	68.9±12.2	0.256
Central PP (mmHg)	39.1±10.7	37.8±14.2	0.690
PWV (m/sec)	**10.28±1.02**	**8.62±1.18**	**0.000**

Data are mean±SD. S/DBP: systolic/diastolic blood pressure, PP: pulse pressure, PWV: pulse wave velocity

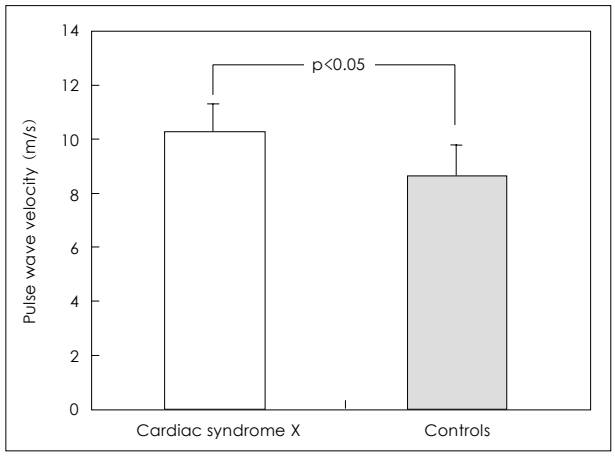

Fig. 2. Comparison of pulse wave velocity between both the groups.

Pulse waveform analysis

The PWV is an indicator of arterial stiffness, which was significantly increased in patients with CSX compared to the controls (10.28±1.02 vs. 8.62±1.18 m/s, respectively, $p<0.05$) (Table 3) (Fig. 2). However, there were no statistical differences in the central blood and central pulse pressures between the groups. A PWV of 9.85 m/s allows for the differentiation between patients with CSX and the controls, with sensitivity and specificity of 65 and 88%, respectively.

Discussion

The present study showed that the arterial stiffness, as measured using the non-invasive measurement of the pulse wave velocity, was increased in patients with cardiac syndrome X compared to the control subjects. Kidawa et al.[15] suggested 8.5 m/s as the cutoff value for the differentiation between CSX and the controls, this value was higher in our study. This discrepancy might have derived from the young aged population, the lack of hypertension history and the carotid-femoral approach used in Kidawa's study.

It has been suggested that arterial stiffness is a precursor of atherosclerosis, or at least a predictor of atherosclerosis.[16] Cardiovascular risk factors have been shown to be positively associated with arterial stiffness,[17][18] and men with angiographically documented CAD have been shown to have stiffer arteries than control subjects.[19][20] Kidawa et al.[15] showed that impairment of the endothelial function and a decreased arterial distensibility may suggest that the vascular abnormalities in syndrome X are a generalized process, similar to those vascular abnormalities observed in the early stages of atherosclerosis. The result from our study on patients with cardiac syndrome X showed an increased PWV, which is a reflection of the increased arterial stiffness. A close relation between an increased PWV and the development of atherosclerosis has been reported.[21][22] Measurements taken in patients with coronary artery disease have shown a decreased compliance of the large arteries. PWV has not been assessed previously in patients with cardiac syndrome X. In our study, we found a significant difference for the PWV between patients with cardiac syndrome X and the controls, and established a PWV cutoff value, with satisfactory specificity and sensitivity, which is useful in the differentiation of these types of patients; PWV measurements provide highly reproducible estimates of the arterial distensibility.

Some studies have suggest that a PWV increase may be used as an early indicator of the development of atherosclerosis, and a significant decrease in the compliance of the large arteries was found in patients with an atherosclerotic risk factor, such as heterozygous familial hypercholesterolemia.[23]

Diastolic dysfunction in CSX patients has been reported previously.[24-26] Dudek et al.[27] found an elevated NT-proBNP level in those patients with cardiac syndrome X, even when the left ventricular systolic function was still preserved. In patients with cardiac syndrome X, an elevated pro-BNP level may contribute to the genesis of microvascular myocardial ischemia, which may ultimately lead to progressive left ventricular dysfunction. Our results also showed a similar finding, in that the pro-BNP level in the CSX group was slightly higher than in the controls, but this was statistically insignificant.

A limitation of this study was the small size of the population sampled; however, well characterized CSX patients fulfilling the stringent entry criteria are not extremely common. Although we tried to exclude patients with coronary artery spasm using a hyperventilation test, the absence of a coronary artery spasm could not be guaranteed. Also, no intravascular ultrasound examinations were performed, which is the ultimate means of visualizing the coronary vascular anatomy. However, our intention was to test non-invasive techniques for analyzing the function of systemic arteries in cardiac syndrome X. Even with intravascular ultrasound technology, subtle anatomical abnormalities in the distal parts of the coronary arteries may go undetected. Finally, these findings do not apply to premenopausal women, due to the additionally increased PWV in postmenopausal women compared to the age-and blood pressure-matched premenopausal women, and the fact that estrogen deficiency may play a major role in the pathogenesis of postmenopausal women with cardiac syndrome X.[28] However, the majority of patients with cardiac syndrome X are postmenopausal women.

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