Assessment of cardio-ankle vascular index in patients with cardiac syndrome-X: an observational study

Kardiyak sendrom X hastalarında kalp-ayak bileği vasküler indeksinin değerlendirilmesi: Gözlemsel bir çalışma

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ABSTRACT

Objective: Arterial stiffness is associated with major adverse cardiovascular events. Cardio-ankle vascular index (CAVI), a novel marker of arterial stiffness, which is weakly influenced by systolic blood pressure, is a sensitive marker the atherosclerosis and arteriolosclerosis. The aim of this study is to investigate arterial stiffness by CAVI in patients with cardiac syndrome X (CSX).

Methods: The present study was observational and cross sectional, and involved 49 patients (26 male) with CSX (angina-like chest pain, positive electrocardiographic ischemic changes at treadmill exercise test, angiographically normal coronary arteries) and 54 healthy subjects (21 male). CAVI was measured by VaSera-1000 CAVI instrument. Statistical analysis was performed using the Chi-square, Student t-test, correlation analysis and logistic regression analysis.

Results: The CAVI and pulse pressure were significantly increased in patients with CSX compared to control group (7.50±1.50, 6.49±0.77, p<0.001; 53.00±10.06, 47.39±8.17, p=0.002, consecutively). In contrast, there were no significant differences in the age, weight, height, body mass index, waist circumference, hip circumference, systolic blood pressure, diastolic blood pressure, mean blood pressure, glucose, low density lipoprotein level, high density lipoprotein level (HDL), triglyceride, estimated creatinine clearance, hemoglobin, left atrium diameter, left ventricular mass (LVM), LVM index and ejection fraction. CAVI was the only independent predictor of CSX in logistic regression analysis (OR=1.780, 95% CI: 1.157-2.737, p=0.009).

Conclusion: CAVI is increased in syndrome X patients and is an independent predictor of this syndrome. *(Anadolu Kardiyol Derg 2013; 13: 766-71)*

Key words: CAVI, arterial stiffness, cardiac syndrome X, coronary, angiography, regression analysis

ÖZET

Amaç: Damar sertliği önemli kardiyovasküler kötü hadiselerle ilişkilidir. Kalp-ayak bileği vasküler indeks ölçümü (KAVI), sistolik kan basıncından çok az etkilenir ve damar sertliği değerlendirilmesinde yeni ve hassas bir yöntem olup ateroskleroz ve arteriolosklerozun hassas bir göstergesidir. Bu çalışmanın amacı kardiyak sendrom-X'li hastalarda (KSX) KAVI yöntemi ile damar sertliğinin değerlendirilmesidir.

Yöntemler: Çalışmamız gözlemsel ve kesitsel nitelikte olup, bu çalışmada 49 KSX (tipik göğüs ağrısı olan, egzersiz elektrokardiyografi testinde pozitif iskemik değişiklikleri bulunan ve yapılan koroner anjiyografide normal koroner arterler tespit edilen hastalar) (29 erkek) ve 54 sağlıklı hasta (21 erkek) değerlendirildi. KAVI VaSera-1000 KAVI aletiyle ölçüldü. İstatistiksel analizde Ki-kare, t-testi, korelasyon analizi ve mantıksal regresyon analizi kullanıldı.

Bulgular: KSX hastalarında KAVI ve nabız basıncı kontrol grubuna göre anlamlı olarak daha yüksekti (sırasıyla 7,50±1,50, 6,49±0,77, p<0,001; 53,00±10,06, 47,39±8,17, p=0,002). Fakat yaş, kilo, boy, vücut kitle indeksi, bel çevresi, kalça çevresi, sistolik kan basıncı, diyastolik kan basıncı, ortalama kan basıncı, düşük ağırlıklı kolesterol, yüksek ağırlıklı kolesterol, trigliserit, kreatinin klirensi, hemoglobin, sol atriyum çapı, sol ventrikül kütlesi, sol ventrikül kütle indeksi ve ejeksiyon fraksiyonları arasında anlamlı fark yoktu. Lojistik regresyon analizinde KSX'in bağımsız öngördürücüsü olarak KAVI bulundu (OR=1,780, %95 CI: 1,157-2,737, p=0,009).

Sonuç: KAVI, KSX hastalarında artış gösterir ve bu hastalığın bağımsız bir göstergesidir. *(Anadolu Kardiyol Derg 2013; 13: 766-71)*

Anahtar kelimeler: KAVI, damar sertliği, kardiyak sendrom X, koroner, anjiyografi, regresyon analizi

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Introduction

Arterial stiffness is associated with major adverse cardiovascular events (1-3). As a result of increased arterial stiffness, systolic blood pressure increases and this leads to ventricular hypertrophy and increased myocardial oxygen demand (4). Increased arterial stiffness is related to coronary atherosclerosis and recurrence of adverse cardiac events (5, 6). Cardio-ankle vascular index (CAVI), a novel marker of arterial stiffness, which is weakly influenced by systolic blood pressure, is a sensitive marker the atherosclerosis and arteriolosclerosis (6-8).

Cardiac syndrome X (CSX) is characterized by the presence of typical chest pain, a positive response to exercise testing, and normal-appearing coronary angiograms (9). The underlying mechanisms are controversial, but myocardial ischemia and increased sympathetic activity may be related. Patients with CSX have an altered autonomic control of the cardiovascular system characterized by impaired baroreceptor sensitivity and sympathovagal imbalance (10, 11).

There are limited data regarding the association between arterial stiffness and CSX in the literature (12, 13). CSX is consequence of coronary microvascular dysfunction (14). Histopathological examinations of endomyocardial biopsies of patients with CSX have shown structural abnormalities of small coronary vessels including medial hypertrophy and luminal narrowing (15). Both endothelium dependent and independent vasodilatation are altered in patients with CSX (16, 17). Vasoconstrictor activity and inflammatory markers are increased in CSX patients (18, 19). Although it is generally accepted as benign condition with favorable prognosis, CSX may be a consequence of generalized process affecting the entire arterial system having variable effects.

Therefore, we investigated the arterial stiffness by with a novel method, cardio-ankle vascular index, in patients with cardiac syndrome X in order to evaluate effect on systemic arterial circulation.

Methods

Study design

The present study is cross-sectional and observational.

Patient population

This study was conducted at outpatient clinic between January 2012 and July 2012. We studied 49 patients (26 male) with cardiac syndrome X (angina-like chest pain, positive electrocardiographic ischemic changes at treadmill exercise test, angiographically normal coronary arteries) and 54 apparently healthy consecutive patients admitted to cardiology outpatient clinic (21 male). Informed consent was obtained from all subjects and the investigation conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by Ethics Committee.

Patients with acute coronary syndrome and previous myocardial infarction, dilated or constrictive cardiomyopathy; metabolic disorders such as insulin dependent diabetes mellitus, non-insulin-dependent diabetes mellitus and insulin resistance syndrome; peripheral arterial disease, moderate to severe valvular heart disease, cerebrovascular disease, atrial fibrillation on 12-channel surface electrocardiography (ECG), atrio-ventricular block of second to third degree; or presence of findings of a post-myocardial infarction, congestive heart failure and renal failure (estimated creatinine clearance <60 mL/min) were excluded from the study. Patients with myocardial bridge and connective tissue disorders were also excluded from the study. Patients having angina pectoris without horizontal ST segment depression and patients with upsloping ST segment depression were excluded from the study.

Basal demographic, clinical and echocardiographic evaluation

Weights of the patients, in light clothes and without shoes, were measured in kilograms, and their heights were also measured. Body mass index (BMI, kg/m^2) was calculated by dividing body weight in kilograms by the square of body height in meters. Waist circumference was measured between the last rib and iliac crest on the midline while the patient was standing. Hip circumference was measured by using the line between the right and left great trochanter of the femur. Transthoracic echocardiographic assessment (Vivid S5 General Electric, Norway) was performed in patients according to the standards of the American Society of Echocardiography. Left ventricular mass (LVM) was calculated according to Devereux formula:

LVM: $0.8 \times 1.04 \times [(LVEDD+IVS+PW)^3 - LVEDD^3] + 0.6$

LVM index: LVM/body surface area

Coronary angiography was performed in patients with cardiac syndrome X by using the standard Judkins technique.

Exercise testing

All patients underwent a standard treadmill exercise stress test (Norav TMX425, FL, USA) using the modified Bruce protocol. Blood pressure, heart rate and 12-lead ECGs were recorded at rest, at one-minute intervals during exercise, at peak exercise, and for at least 3 minutes in the recovery phase. The ECG and ST-segment depression were continuously displayed and measured automatically by a computer-assisted in all 12 leads. Only leads I, II, III aVL, aVF, and V2 to V6 were used for analysis. An exercise test (Bruce protocol) was said to be positive if there was at least 0.2 mV of horizontal ST segment depression. The electrocardiography exercise test was aborted if the heart rate reached submaximal values, patients were complaining of chest pain, cardiac arrhythmias (non-sustained ventricular tachycardia; new onset of atrial fibrillation, atrial flatter, or of a supraventricular tachycardia) were observed, or criteria for a positive electrocardiography test were reached. Patients were encouraged to perform their maximum effort.

Cardiac catheterization

Coronary angiograms (Siemens Axiom Artis, Germany) were performed with a femoral approach using the Judkins technique

without the use of nitroglycerin, adenosine or a calcium channel blocker. Coronary angiograms were judged with regard to smooth appearance, luminal wall irregularities, epicardial local or diffuse caliber reduction and stenosis. 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, during coronary angiography all patients underwent a hyperventilation test, which was performed by asking the patients to breathe quickly and deeply for 5 min.

Blood pressure and cardio-ankle vascular index measurements

Blood pressure was measured, in compliance with World Health Organization guidelines, by using a mercury sphygmomanometer (ERKA, Germany) with a cuff appropriate to the arm circumference, in patients at rest for 20 minutes (Korotkoff phase I for systolic blood pressure and V for diastolic blood pressure).

Pulse pressure=systolic blood pressure-diastolic blood pressure

Mean blood pressure=systolic blood pressure + 2 X diastolic blood pressure/3

CAVI was measured using a VaSera VS-1000 CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan). CAVI was measured in the morning after 15 minutes of rest. Briefly, cuff was applied to the bilateral upper arms and ankles, with the subject supine and the head held in the midline position. Electrocardiography, phonocardiography and pressures and waveforms of brachial and ankle arteries were measured and pulse wave velocity and subsequently CAVI were calculated automatically. CAVI measurements were performed by experienced cardiologist who blinded to spirometric test.

CAVI is determined by the following equation (8):

CAVI: $a[(2r/\Delta P) \times \ln(Ps/Pd)PWV^2]+b$

Where Ps and Pd are systolic blood pressure and diastolic blood pressure, respectively, PWV is pulse wave velocity from the origin of the aorta to the junction of the tibial artery with the femoral artery, ΔP is Ps-Pd (systolic blood pressure- diastolic blood pressure), r is blood density and a and b are constants. The equation is derived from Bramwell-Hill's equation and the stiffness parameter β, and CAVI was adjusted for blood pressure based on the stiffness parameter β. Therefore, CAVI reflects the stiffness of the aorta, femoral artery and tibial artery as a whole; theoretically, it is not affected by blood pressure (8). After automatic measurements, the obtained data were analyzed using VSS-10 software (Fukuda Densi) and the values of right and left CAVI were calculated. The average of the right and left CAVIs was used for analysis.

Statistical analysis

SPSS 17.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Continuous variables are expressed as mean±standard deviation (SD) and categorical variables are expressed as percentage. An analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. Comparisons of continuous variables were performed using the unpaired Student t-test and categorical variables were compared with the Chi-square test. The Pearson correlation analysis was used for assessing correlates of CAVI. Variables with p value ≤0.10 criteria were selected for logistic regression analysis. Logistic regression analysis was performed in order to find independent associates of cardiac syndrome x. A p value of ≤0.05 was considered statistically significant.

Results

Clinical characteristics of study population

The CAVI was increased in patients with CSX compared to control group (7.50±1.50, 6.49±0.77, p<0.001 consecutively). Pulse pressure (PP) was significantly higher in CSX group compared to controls (53.00±10.06, 47.39±8.17, p=0.002 successively) (Fig. 1).

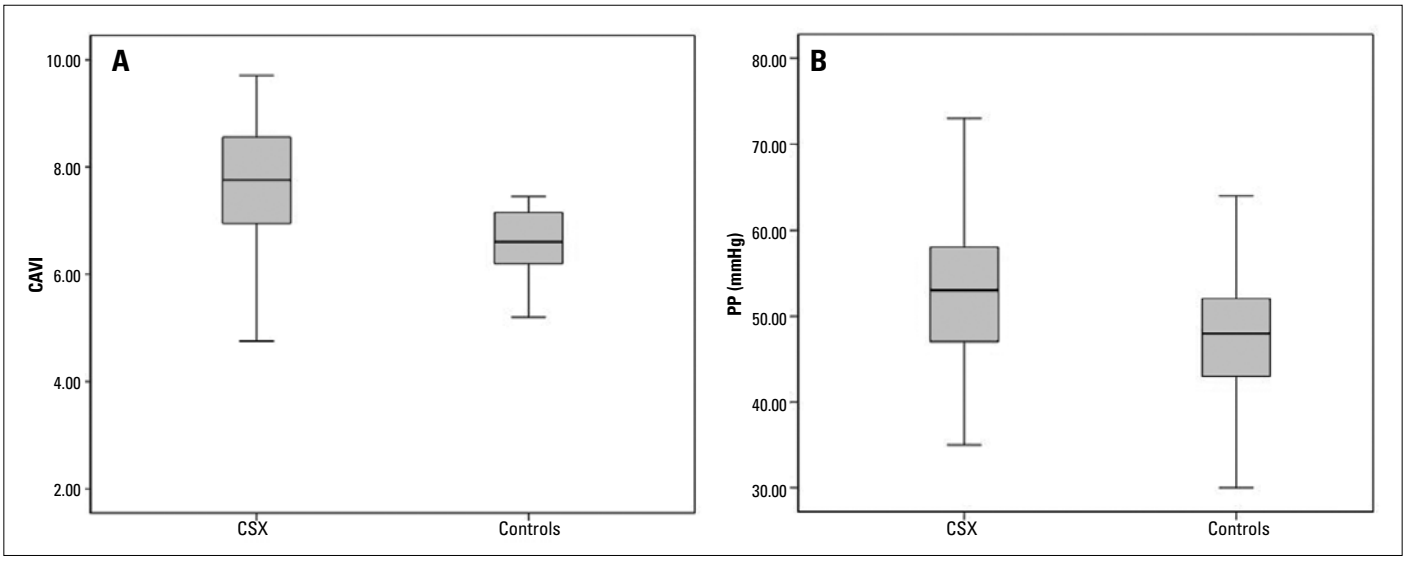

Figure 1. A. Box plot shows the CAVI values of CSX and controls. B. Box plot shows the PP levels of CSX and controls
CAVI - cardio-ankle vascular index, CSX - cardiac syndrome X, PP - pulse pressure

Table 1. Patient characteristics

Variables	CSX (n=49)	Control group (n=54)	*p
Age, years	57.73±6.95	55.07±10.43	0.135
Male, n (%)	26 (53.1)	21 (38.9)	0.149
Hypertension, n (%)	12 (24.5)	11 (20.4)	0.616
Hyperlipidemia, n (%)	6 (12.2)	11 (20.4)	0.267
Smoking, n (%)	15 (30.6)	18 (33.3)	0.768
ACE/ARB, n (%)	9 (18.4)	7 (13.0)	0.450
Beta-blocker, n (%)	5 (10.2)	1 (1.9)	0.082
Ca^{++} channel blockers, n (%)	4 (8.2)	2 (3.7)	0.420
Nitrate, n (%)	3 (6.1)	0 (0)	0.104
Statin, n (%)	6 (12.2)	5 (9.3)	0.624
BMI, kg/m^2	29.25±5.79	31.13±6.50	0.125
Waist circumference, cm	96.78±15.02	94.96±17.18	0.572
Hip circumference, cm	102.61±13.65	103.24±9.75	0.787
Systolic BP, mmHg	138.47±12.41	133.46±13.53	0.054
Diastolic BP, mmHg	85.47±10.98	86.07±9.39	0.764
MAP, mmHg	103.14±10.45	101.87±10.24	0.536
PP, mmHg	53.00±10.06	47.39±8.17	0.002

Data are presented as number (percentage), mean ±standard deviation
*Independent samples t-test and Chi-square test
ACE/ARB - angiotensin converting enzyme inhibitor/angiotensin receptor blocker, BP - blood pressure, CSX - coronary syndrome X, MAP - mean arterial pressure, PP - pulse pressure

Table 2. Laboratory, echocardiography and CAVI data

Variables	CSX (n=49)	Control group (n=54)	*p
Glucose, mg/dL	98.21±11.69	96.13±13.42	0.407
LDL, mg/dL	138.87±30.79	130.20±32.55	0.169
HDL, mg/dL	49.84±12.71	46.04±10.28	0.097
Triglyceride, mg/dL	155.84±73.26	138.78±64.65	0.212
eCcl, mL/min	109.90±39.19	120.34±37.38	0.170
Hemoglobin, gr/L	13.69±1.49	13.47±1.43	0.450
LA, mm	35.14±5.50	35.37±5.90	0.840
LVM, gr	218.80±69.61	222.97±125.22	0.837
LVM index, gr/m^2	114.21±34.83	117.17±65.21	0.777
EF, %	64.43±8.47	62.06±9.04	0.176
CAVI	7.50±1.50	6.49±0.77	<0.001

Data are presented as number (percentage), mean ±standard deviation
*Independent samples t-test.
CAVI - cardio-ankle vascular index, CSX - coronary syndrome X, eCcl - estimated creatinine clearance, EF - ejection fraction, HDL - high density lipoprotein, LA - left atrial diameter, LDL - low density lipoprotein, LVM - left ventricular mass

Table 3. Results of logistic regression analysis

Variables	p	OR	95% CI
CAVI	0.009	1.780	1.157-2.737
PP	0.065	1.049	0.997-1.104
HDL	0.159	1.028	0.989-1.069
B-blocker	0.644	1.723	0.171-17.357

B-blocker - beta blocker, CAVI - cardio-ankle vascular index, CI - confidence interval, HDL -high density lipoprotein, OR - odds ratio, PP - pulse pressure

In contrast, there were no significant differences in the age, weight, height, body mass index (BMI), waist circumference, hip circumference, systolic blood pressure, diastolic blood pressure, mean blood pressure, glucose, low density lipoprotein level, high density lipoprotein level (HDL), triglyceride, estimated creatinine clearance, hemoglobin, left atrium diameter, LVM, LVM index and ejection fraction (EF) (Tables 1, 2). Frequency of hypertension, hyperlipidemia and smoking habit were similar between groups.

Relationship of CAVI with clinical variables

CAVI was correlated weakly with BMI, EF and PP (r=-0.220, p=0.026, r=0.230, p=0.019 and r=0.340 p<0.001 consecutively).

Independent predictors of CSX

CAVI, PP, HDL and usage of beta -blockers were included in the logistic regression analysis. CAVI was the only independent predictor of CSX in logistic regression analysis (OR=1.780, 95% CI: 1.157-2.737, p=0.009) (Table 3).

Discussion

We found that CAVI and PP were increased in patients with CSX compared to controls. Logistic regression analysis showed that CAVI was the independent predictor of CSX. To our knowledge it is the first study in the literature evaluated CAVI in patients with CSX. CAVI differs from other arterial stiffness measurement methods by independence of blood pressure. Furthermore, in contrary to other methods of arterial stiffness measurements including pulse wave velocity, augmentation index and aortic elastic properties, CAVI is not a regional stiffness parameter instead reflects the stiffness of whole arterial tree. Recent studies have shown that CAVI is correlated with subclinical parameters of atherosclerosis including carotid intima media thickness and epicardial fat thickness (20-22).

Among patients with chest pain who are referred for coronary angiography, 15-20% has normal vessels (23). CSX is characterized by angina pectoris, a positive response to exercise testing, and normal-appearing coronary angiograms with no spontaneous or inducible epicardial coronary artery spasm on provocation tests (9). Ergonovine, hyperventilation and acetylcholine provocation can test for epicardial coronary vasospasm, which establishes the diagnosis of variant angina. Moreover, recent studies have shown that, intracoronary acetylcholine can also detect coronary endothelial dysfunction, which appears to identify patients with chest pain and normal coronary angiograms in patients without epicardial coronary artery spasm (24). In contrary to our study it is generally accepted that, CSX affects

women (25). But in a recent large scale analysis, Vermeltfoort et al. (26) reported that CSX was also common among men as 44% of the CSX population was men. This finding may be incidental or associated with our strict exercise test criteria as we excluded patients with only angina and/or upsloping ECG depression in our study. As exercise angina is a common finding among women. Horizontal and down sloping depression of ST segments are more specific for stenotic coronary artery disease than upsloping depression and angina pectoris (27). Therefore we decided to include patients with horizontal and down sloping ST segment depression at exercise ECG test.

Increased pulse wave velocity in CSX was described previously (12, 13). Lekakis et al. (28) reported that patients with CSX had similar endothelial dysfunction of peripheral arteries like patients with extended coronary artery disease. Impaired endothelial function and a significant rise in arterial wall stiffness resulted in increased arterial resistance and decreased compliance in patients with CSX consequently increased CAVI. Generalized atherosclerosis of aorta resulting in decreased compliance may cause attenuated coronary blood flow thus ischemic heart disease in these patients. Low coronary inlet resting pressure secondary to abnormal flow pattern in ascending aorta was shown in patients with CSX (29).

Atherosclerosis affects not only coronary circulation but also vascular tree. Atherosclerosis of aorta and major branches is associated with decreased aortic distensibility and increased arterial stiffness (30, 31). The decrease in aortic distensibility may increase the impedance to left ventricular ejection fraction and then reduce the effective coronary blood flow. Consequently, deterioration of diastolic functions (32). In some studies, hypertension and arteriosclerotic risk factors have been shown to affect arterial stiffness (33). CAD risk factors, including hypercholesterolemia, obesity, smoking hypertension, often present in patients with CSX and may contribute to the arterial stiffness.

In our study presence of hypertension, level of blood pressure, smoking status, anthropometric measurements were similar between groups. Although it is generally accepted as benign condition with favorable prognosis, our results supported that CSX may be a consequence of generalized process effecting the arterial system causing increased arterial stiffness.

Study limitations

We did not perform intravascular ultrasonography and optical coherence tomography to assess coronary anatomy. However, intravascular ultrasonography and optical coherence tomography may also misinterpret the distal coronary artery disease. Although ergonovine test is superior to the hyperventilation test, we preferred to use the hyperventilation test instead of the ergonovine injection to rule out the coronary spasm in patients with CSX, because of the possibility of persistent and severe, painful spasm with ergonovine. Another limitation of our study was the relatively small patient population, thus large scaled studies are further required to confirm our findings.

Conclusion

CAVI is increased in syndrome X patients and is an independent predictor of this syndrome.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - A.Ç.A., T.G.; Design - A.Ç.A.; Supervision - M.Y., Ş.Ç.; Resource - İ.G., T.T., F.B., A.C.A., T.G.; Data collection&/or Processing - A.Ç.A., T.G., F.B.; Analysis &/or interpretation - A.Ç.A., D.A.A.; Literature search - A.Ç.A., D.A.A.; Writing - A.Ç.A., D.A.A.; Critical review - Ş.Ç., M.Y.; Other - T.G.

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