Relationship of aortic knob width with cardio-ankle vascular stiffness index and its value in diagnosis of subclinical atherosclerosis in hypertensive patients: a study on diagnostic accuracy

Hipertansif hastalarda aortik topuz genişliği ile kardiyo - ayak bileği vasküler indeks arasındaki ilişki ve aortik topuzun subklinik aterosklerozun tanısındaki yeri: Bir tanısal değeri çalışması

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ABSTRACT

Objective: The aim of our study was to determine the usefulness of the aortic knob width (AKW) in the assessment of subclinical atherosclerosis in hypertensive patients.
Methods: In this study on diagnostic accuracy, 374 consecutive hypertensive patients with at least one cardiovascular risk factor were enrolled. AKW was measured on chest X-ray. Cardio-ankle vascular index (CAVI) was measured by VaSera-1000 CAVI instrument. The diagnostic value of AKW was assessed using ROC analysis.
Results: There was a significant correlation between aortic knob width and CAVI (r=0.45, p<0.001), age (0.39, p<0.001), systolic (r=0.17, p<0.001), diastolic (r=0.23, p<0.001) and mean (r=0.2, p<0.001) blood pressures. In linear regression analysis CAVI (β=0.3, 95% CI 0.33-0.98, p<0.001), age (β=0.3, 95% CI 0.09 - 0.21, p<0.001) and diastolic blood pressure β=0.2, 95% CI 0.08-1.9, p<0.001) were independently associated with AKW. It was significantly higher in patients with subclinical atherosclerosis (CAVI ≥9) than borderline (8 ≤CAVI <9) (41.4±5.5 versus 36.7±5.3 mm, p<0.001) and healthy (CAVI <8) subjects (41.4±5.5 versus 35.5±4.3 mm, p<0.001). Analysis using the ROC curve has demonstrated that aortic knob of 41 mm constitutes the cut-off value for the presence of subclinical atherosclerosis with 71% sensitivity and 77% specificity (AUC-0.67, 95% CI 0.51-0.82).
Conclusion: Observation of aortic knob on chest X-ray in hypertensive patients may provide important predictive information of subclinical atherosclerosis. *(Anadolu Kardiyol Derg 2012; 12: 102-6)*
Key words: CAVI, subclinical atherosclerosis, aortic knob, diagnostic accuracy, sensitivity, specificity

ÖZET

Amaç: Bu çalışmanın amacı göğüs grafisinde aort topuz genişliğinin (ATG) hipertansif hastalarda subklinik aterosklerozun bir göstergesi olup olmadığını araştırmaktır.
Yöntemler: Hipertansif ve en az bir tane kardiyovasküler risk faktörü olan 374 hasta bu tanısal değeri çalışmaya alındı. Kardiyo-ayak bileği vasküler indeksi (CAVI) VaSera VS-1000 cihazı ile değerlendirildi. Aort topuz genişliği göğüs grafisinde ölçüldü. ATG'nin tanısal değeri ROC analizi ile değerlendirildi.
Bulgular: Aort topuz genişliği ile CAVI arasında istatistiksel olarak anlamlı bir ilişki vardı (r=0.45, p<0.001). Ayrıca, yaş (0.39, p<0.001), sistolik kan basıncı (r=0,17, p<0.001), diyastolik (r=0.23, p<0.001) ve ortalama kan basıncı (r=0.2, p<0.001) ile CAVI arasında anlamlı bir ilişki bulundu. Lineer regresyon analizinde CAVI (β=0.3, %95 GA 0.33-0.98, p<0.001), yaş (β=0.3, %95 GA 0.09-0.21, p<0.001) ve diyastolik kan basıncı (β=0.2, %95 GA 0.08-1.9, p<0.001) ile ATG arasında bağımsız bir ilişki vardı. ATG subklinik aterosklerozu olanlarda (CAVI ≥9) sınırda anormal (8 ≤ CAVI <9) (41.4±5.5 karşı 36.7±5.3 mm, p<0.001) ve normal olanlara (CAVI <8) (41.4±5.5 karşı 35.5±4.3 mm, p<0.001) göre anlamlı olarak yüksekti. ROC analizinde aortik topuzun 41 mm olması subklinik atherosklerozu %71 duyarlılık ve %77 özgüllük ile tespit edebiliyordu (EAA 0.67, %95 GA 0.51-0.82).
Sonuç: Göğüs grafisinde aortik topuzun değerlendirilmesi hipertansif hastalarda subklinik aterosklerozun varlığı ile ilgili bilgi sağlayabilir. *(Anadolu Kardiyol Derg 2012; 12: 102-6)*
Anahtar kelimeler: CAVI, subklinik ateroskleroz, aort topuzu, tanısal değer, duyarlılık, özgüllük

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Introduction

Stiffness of large arteries has been related to cardiovascular mortality. Cardio-ankle vascular index (CAVI) is considered to reflect arteriosclerosis of the aorta and is a novel parameter of arterial stiffness and surrogate marker of subclinical atherosclerosis (1). It is widely accepted that an increase in arterial stiffness leads a premature return of reflected waves in late systole, increasing central pulse pressure, thus systolic blood pressure (SBP). SBP increases the load on the left ventricle (LV), increasing myocardial oxygen demand. Moreover, arterial stiffness is associated with left ventricular hypertrophy (LVH) (2).

Arterial disease does not begin with the first clinical event but develops long before without symptoms. However, traditional risk factors are poor screening tests for coronary heart disease (CHD) (3). Identifying asymptomatic individuals with subclinical arterial disease may be considered as the best current screening test for predicting subsequent CHD events and offering them aggressive risk reduction therapy. Therefore, in recent years, great emphasis has been placed in order to identify patients with subclinical atherosclerosis (4-6).

The aortic knob is a radiographic structure that is formed by the foreshortened aortic arch and a portion of the descending aorta. Rayner et al. (7) demonstrated increased diameter of aortic knob in hypertensive patients compared to normotensive subjects and its correlation age and other markers of target organ damage. In addition, aortic dilatation was regarded as a representative marker of atherosclerotic process (8). However, the knowledge on association between AKW and subclinical atherosclerosis is lacking.

Therefore, in present study, we aimed to investigate the relation between AKW and CAVI in order to determine whether increased AKW would reflect subclinical atherosclerosis in asymptomatic hypertensive patients.

Methods

Study design and patients

This study on diagnostic accuracy was conducted at Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital. Patients with hypertension and having at least one cardiovascular risk factor were enrolled consecutively. Patients were excluded if they had established cardiovascular disease or symptoms, heart failure, moderate to severe valvular heart disease, chronic renal failure. Moreover, we excluded patients whose chest X-ray was not properly centered, if there was any deviation of the trachea or shift of the mediastinum, and if there was any known disease and the aorta such as aortitis.

Patients divided into three groups according to the CAVI values. CAVI <8 demonstrates normal, whereas CAVI ≥9 reflects subclinical atherosclerosis. CAVI ≥ 8 to < 9 is considered borderline (9-12). Numbers of patients with normal, borderline and abnormal CAVI values were 117, 121 and 136, respectively.

All patients gave informed consent before enrollment and the study protocol was approved by Ethics Committee.

Laboratory analyses

After an overnight fast, a sample of blood was collected to measure routine chemistry including serum creatinine, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

Assessment of aortic knob width

All patients had chest radiography in the postero-anterior (PA) view. An examiner who was unaware of the result of the patient's arterial stiffness measurement reviewed the chest radiography. The widest point of the ascending aortic knob was measured along the horizontal line from the point of the lateral edge of the trachea to the left lateral wall of the aortic knob (Fig. 1).

Assessment of CAVI

CAVI was measured using a VaSera VS-1000 CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan) by the methods described previously (9). CAVI was measured in the morning after 12 hours of fasting. Briefly, cuff was applied to the bilateral upper arms and ankles, with the subject supine and the head held in the midline position. After resting for 10 minutes, measurements were performed. Electrocardiography, phonocardiography, and pressures and waveforms of brachial and ankle arteries were measured. Thereafter, cardio-ankle pulse wave velocity (ca- PWV) and subsequently CAVI were calculated automatically. According to the manufacturer company recommendations, CAVI was considered normal (CAVI <8), borderline (8 ≤CAVI <9) and abnormal (CAVI ≥9). Abnormal CAVI represents subclinical atherosclerosis (10).

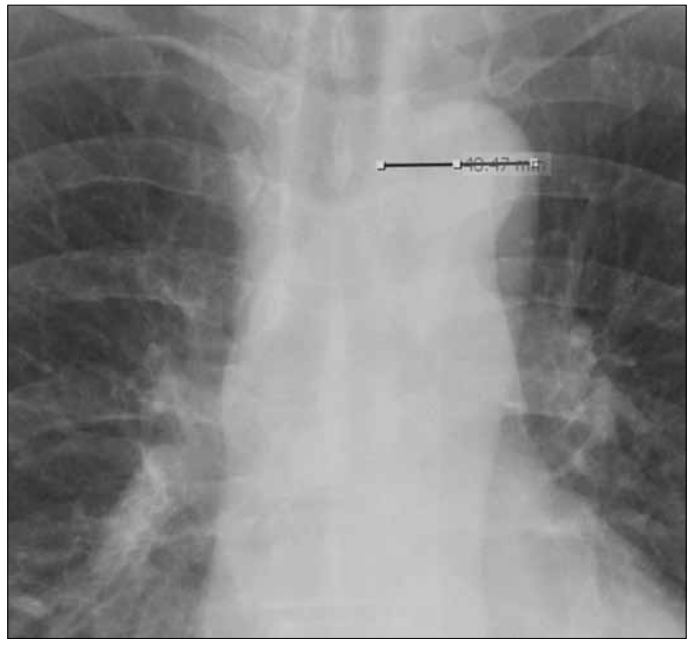

Figure 1. Chest X-Ray view of aortic knob width assessment

Statistical analysis

Statistical analysis was done by using SPSS 14.0 statistical software (SPSS Inc., Chicago, IL, USA). 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. The Pearson and Spearman correlation analysis were used for assessing correlation between AKW and other variables. Variables meeting a p value ≤0.1 criterion were selected for linear regression analysis. Linear regression analysis was performed in order to find independent associates of AKW. Also, Kruskal-Wallis test was performed to compare AKW values in three groups. Mann-Whitney U test was used as post hoc test in order to compare AKW values between two groups.

ROC curve analyze was done to determine sensitivity and specificity of aortic knob value in subclinical atherosclerosis. A p value of ≤0.05 was considered statistically significant.

Results

Clinical and demographic characteristics of patients are illustrated in Table 1.

Relationship of AKW with clinical variables

There was a significant correlation between AKW and CAVI (r=0.45, p<0.001), age (0.39, p<0.001), systolic (r=0.17, p< 0.001), diastolic (r=0.23, p<0.001) and mean (r=.2, p<0.001) blood pressures (Table 2, Fig. 2). In linear regression analysis CAVI (β=0.3, 95%CI 0.33-0.98, p<0.001), age (β=0.3, 95% CI 0.09-0.21, p<0.001) and diastolic blood pressure (β=0.2, 95% CI 0.08-1.9, p<0.001) were independently associated with AKW (Table 3).

AKW and characteristics of subclinical atherosclerosis

AKW was significantly higher in patients with subclinical atherosclerosis than borderline (41.4±5.5 versus 36.7±5.3, p<0.001) and subjects with normal CAVI value (41.4±5.5 versus 35.5±4.3, p<0.001). There was no difference in AKW between borderline and normal CAVI groups (36.7±5.3 versus 35.5±4.3, p=0.19) (Fig. 3).

Diagnostic accuracy of AKW in subclinical atherosclerosis

Analysis using the ROC curve has demonstrated that aortic knob of 41 mm constitutes the cut-off value for the presence of subclinical atherosclerosis with 71% sensitivity and 77% specificity (AUC-0.67, 95% CI 0.51-0.82) (Fig. 4).

Discussion

In present study, we found significant and independent association between AKW and CAVI. Also, age and diastolic blood pressure were significantly and independently correlated with AKW.

Several alterations in vascular structure have been described in patients with systemic hypertension (12-16) and most cardiovascular events are the consequence of a progressive vascular disease. This disease begins at an early age and progresses with structural remodeling. Noninvasive assessment of the arterial vasculature seems important since biological process in the artery wall is a better guide to predict cardiovascular morbid events than standard risk factors (17, 18).

There are multiple noninvasive methods and techniques that can identify subclinical atherosclerosis, and arterial stiffness is one of them. CAVI is measured easily and noninvasively and is a new index of arterial stiffness that is independent of blood pres-

Table 1. Baseline characteristics of study population

Variables	n=374
Age, years	63±10
Gender (M/F), (%)	44/56
Dyslipidemia, n (%)	205 (55)
Diabetes, n (%)	127 (34)
Smoking, n (%)	201 (54)
Systolic pressure, mmHg	159±22
Diastolic pressure, mmHg	95±10
Pulse pressure, mmHg	63±18
Mean pressure, mmHg	121±14
Aortic knob width, mm	38±6
CAVI	8.6±1.7
Cardiovascular medication	
ACEI and ARB, n (%)	220 (59)
Beta- blockers, n (%)	112 (30)
Ca++ channel blockers, n (%)	153 (41)
Cholesterol lowering therapy, n (%)	176 (47)
Diuretics, n (%)	183 (49)
Oral antidiabetics, n (%)	67 (18)

Data are expressed as mean±SD and number (percentage)
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker, CAVI - cardio - ankle vascular index, Ca - calcium, F - female, M - male

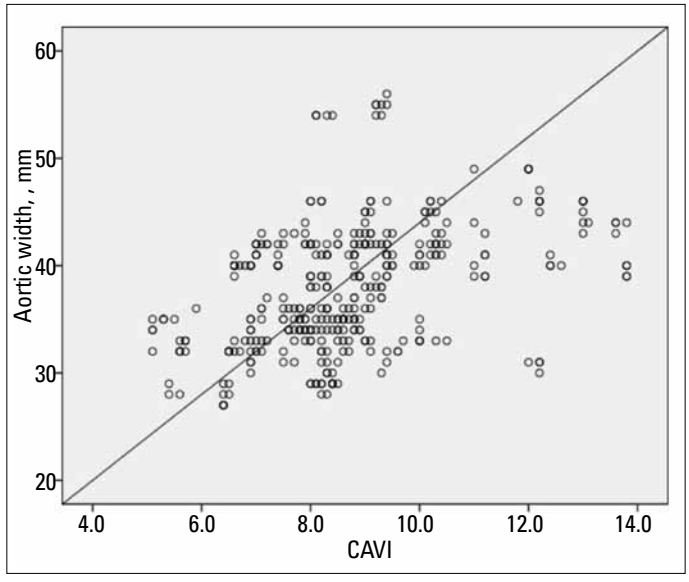

Figure 2. Correlation between CAVI and aortic knob width (Spearman`s coefficent r=0.45, p<0.001)
CAVI - cardio-ankle vascular stiffness index

Table 2. Correlations of clinical variables and aortic knob width

Variables	r	p
Age	0.39	<0.001
Gender	0.09	0.1
Dyslipidemia	0.06	0.2
Diabetes	0.06	0.3
Smoking	0.08	0.3
Systolic pressure	0.17	<0.001
Diastolic pressure	0.23	<0.001
Pulse pressure	0.04	0.5
Mean pressure	0.2	<0.001
CAVI	0.45	<0.001
Cardiovascular medication		
ACEI and ARB	0.1	0.9
Beta blockers	0.09	0.1
Ca channel blockers	0.11	0.7
Cholesterol lowering therapy	0.07	0.6
Diuretics	0.02	1
Oral antidiabetics	0.12	0.4

Spearman and Pearson's correlation analyses
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker, CAVI - cardio ankle vascular index

Table 3. Analysis of variables associated with increased width of aortic knob

Variables	β	95% CI	p
Age	0.3	0.09-0.21	<0.001
Systolic pressure	0.08	-1.7-0.4	0.3
Diastolic pressure	0.2	0.08-1.9	<0.001
Mean pressure	0.2	-0.15-1.7	0.08
CAVI	0.3	0.33-0.98	<0.001

Linear regression analysis
CAVI - cardio ankle vascular index, CI - confidence interval

sure (1). Okura et al. (19) demonstrated significant correlation between CAVI and carotid intima-media thickness, other well-known surrogate marker of subclinical atherosclerosis, and suggested that CAVI was a useful clinical marker for evaluating subclinical atherosclerosis in patients with essential hypertension. In addition, Nakamura et al. (20) showed that CAVI was significantly and strongly associated with the presence and severity of coronary atherosclerosis.

The aorta undergoes marked changes with normal aging and these changes are due predominantly to alterations in the structural and physical properties of the arterial wall (20). Age is a major pathobiological determinant of aortic dilatation (21). In addition; body surface area, gender, and hypertension were directly associated with thoracic aorta dimensions (22). Also, ascending aortic diameter was positively correlated with Framingham risk score, coronary artery calcification and

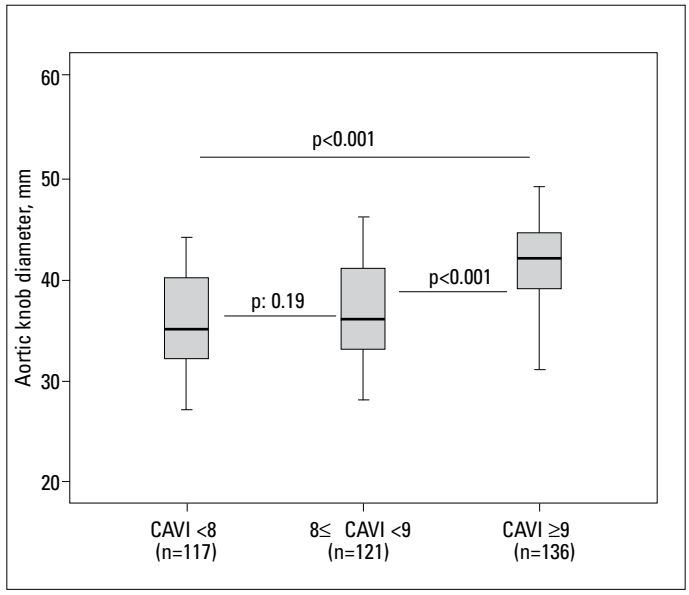

Figure 3. Differences in AKW throughout CAVI groups
Kruskal-Wallis test Chi-square=61,2, p for trend <0.001; Mann-Whitney U test for between groups difference is significant for normal and subclinical atherosclerosis p<0.001
AKW - aortic knob width, CAVI - cardio-ankle vascular stiffness index

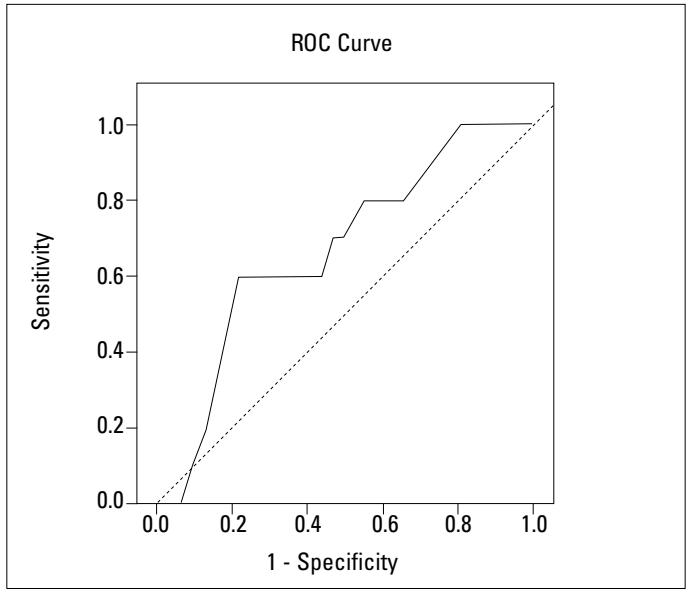

Figure 4. ROC analysis of AKW value in diagnosis of subclinical atherosclerosis (AUC- 0.67, 95% CI 0.51 - 0.82, p<0.001)
AKW - aortic knob width

regarded as a representative marker of generalized atherosclerotic process (23).

Study limitations

There are several limitations of our study. First of all, we included only hypertensive patients. Therefore, our results cannot be incorporated to general population. In addition, our study is cross sectional and we cannot determine whether patients with increased aortic knob diameter will end up high rate of cardiovascular events. Although relation between CAVI and aortic knob

width was statistically significant, this correlation was mild to moderate. It may be explained by the fact that CAVI represents a regional index including a large part of the vasculature system whereas the aortic knob width measurement seems to be related to a much localized part of the aorta. In addition, the main purpose of our study was to know whether there was a correlation between CAVI and aortic knob width. Detailed pathophysiological mechanisms explaining this correlation was beyond of this study's aim and deserve further investigation.

Conclusion

Although this study is purely correlative and no causative conclusions can be drawn, it can be postulated that increased aortic knob width could reflect increased arterial stiffness in subjects with hypertension. Chest X ray is cheap, readily available and can be evaluated by every physician easily. Therefore, observation of aortic knob may be helpful in detecting asymptomatic hypertensive patients with subclinical atherosclerosis who should require aggressive interventions and appropriate pharmacotherapy.

Conflict of interest: None declared.

Authorship contributions: Concept -L.K., H.E.; Design - A.A.K.; Supervision - L.K., H.E., A.R.A.; Resources - A.A., H.B., Z.A., M.T.A.; Material - H.B.; Data collection&/or Processing - Ş.Ç., A.A.K.; Analysis &/or Interpretation - L.K., H.E.; Literature Search - Z.A., Ş.Ç.; Writing - A.R.A, L.K., M.T.A.; Critical review - A.R.A., Z.A., H.B.; Other - A.A.

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