

Original Article

Feasibility and Clinical Significance of Echocardiographic Assessment of Aortic Root Compliance in Hypertensive Patients

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ABSTRACT

Objectives: To evaluate the hypothesis that hypertension is associated with reduced aortic compliance and the stiff aortic root is a marker for prediction of associated coronary artery disease (CAD).

Design: Cohort study conducted between January 2003 and July 2005.

Setting: Non-invasive cardiac laboratory, Department of Medicine, Farwania Hospital, Kuwait.

Patients and Methods: One hundred and forty hypertensive patients and 30 normotensive subjects were included in the study. All patients underwent a 24-hour ambulatory blood pressure recording, hand-grip isometric exercise echocardiography and treadmill exercise ECG test. Only 100 hypertensive patients were known to have undergone coronary angiography in the course of their clinical management and were classified into two subgroups; group Ia: included 60 patients with CAD and group Ib: included 40 patients with normal coronary angiography.

Results: There was a significant increase in aortic root area ($p < 0.05$) in the normotensives after isometric exercise but no significant change ($p = NS$) in the hypertensive patients. There was a significant reduction

in aortic root compliance ($p < 0.05$) in the hypertensive patients than the subjects with normal blood pressure and in the hypertensive patients with CAD than the hypertensive patients with normal coronary angiography ($p < 0.05$). There was a significant correlation between the blood pressure load as an independent variable and the aortic root compliance as a dependent variable ($r = 0.873$, $p < 0.05$). Predictive indices revealed that reduced aortic root compliance is valid as an indicator for the prediction of CAD as compared to ischemic heart disease (sensitivity = 69% Vs 60%, specificity = 71% Vs 67%, accuracy = 70% Vs 60.7%, positive predictive value = 81.8% Vs 46.2% and negative predictive value = 55.5% Vs 73.3%, respectively). Stepwise multivariate analysis revealed a significant relationship between age, gender, smoking status and hypercholesterolemia and reduced aortic root compliance in hypertensive patients ($p < 0.05$).

Conclusion: Aortic root compliance is compromised in the hypertensive patients when compared with normotensives subjects and its detection is of clinical significance as the stiff aortic root can be considered a marker for prediction of the associated CAD.

KEY WORDS: aortic root, isometric exercise, transthoracic echocardiography

INTRODUCTION

Aorta functions not only as a conduit delivering blood to the tissues but as an important modulator of the entire cardiovascular system, buffering the intermittent pulsatile output from the heart to provide steady flow to capillary beds^[1]. By virtue of its elastic properties aorta influences left ventricular function and coronary blood flow^[2]. Systemic hypertension, a common disorder with potentially serious complications, exerts further ill effects through structural and functional modifications of the arterial wall^[3]. Previous studies using different techniques have shown that aortic elastic properties are compromised in patients with arterial hypertension^[4]. Roy^[5] reported that atherosclerotic plaques were present diffusely in

coronary artery disease of all adult necropsied patients whether with or without symptomatic ischemic heart disease and similar complicated atherosclerotic plaques were present in the aorta as well. Stefanadis *et al* from University of Athens, Greece described a method of obtaining aortic pressure-diameter relationship in conscious humans. With this method, aortic diameters were acquired with a high-fidelity intravascular catheter developed in our institution that has an ultrasonic displacement meter at its distal end. Aortic pressures were acquired simultaneously and at the same aortic level with a catheter-tip micromanometer^[6]. Measurement of pulse wave velocity has been extensively used providing only indirect estimations of the elastic properties of the aorta^[7].

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The aims of the study were to:

1. Evaluate the aortic root compliance in hypertensive patients by echocardiogram.
2. Study the association of CAD and reduced aortic root compliance.
3. Investigate the validity and reliability of aortic root compliance to predict the associated CAD.

PATIENTS AND METHODS

Study patients:

One hundred and forty hypertensive patients and 30 control subjects were included in the study. All patients were referred by their physicians to the cardiology clinic at Farwania Hospital with a blood pressure more than 140/90 mmHg. All patients were evaluated clinically by looking at history, physical examination, 12-leads ECG and routine laboratory investigations.

Exclusion criteria included patients with history of myocardial infarction, unstable angina, left main CAD, three vessel disease, intraventricular conduction disturbances, strain patterns due to left ventricular hypertrophy, atrial fibrillation, frequent ventricular ectopics, retinopathy, nephropathy, diabetes mellitus, cerebrovascular disease, significant valvular disease and pregnant women.

Exclusion was based on: medical history, physical examination, fundus examination, urine analysis for proteinuria and 12-lead electrocardiogram to avoid confounding factors.

There were two groups:

- Group I: included 140 hypertensive patients (120 males and 20 females)
- Group II: included 30 normotensive control subjects (25 males and 5 females)

Coronary angiography:

Only 100 hypertensive patients were known to have undergone coronary angiography in the course of their clinical management and were classified into two subgroups:

1. Group Ia: included 60 hypertensive patients with angiographically documented coronary artery disease.
2. Group Ib: included 40 hypertensive patients with normal coronary angiography.

Blood pressure measurements:

Mercury sphygmomanometer was used to measure office systolic and diastolic BP (mmHg). At least two measurements were recorded between 8 and 11 am with the patients in a sitting position with the legs uncrossed and the feet on the floor. Patients were requested to refrain from heavy exercise in the morning and to avoid cola drink,

coffee, tea and smoking for at least one hour before the measurement. BP was measured after the patients had rested for 15 minutes. The last five minutes of rest were spent in the measurement room with the cuff around the right upper arm. Cuff inflation pressure was then determined by palpating the disappearance and appearance of the radial pulse.

Ambulatory blood pressure was recorded with an auscultatory device (Accutracker II). Correct position of the microphone was identified by palpating the brachial artery. Ambulatory BP was recorded during daytime (6 am to 10 pm) at one-hour intervals and during the night (10 pm to 6 am) at 2-hour intervals. Sleep time was identified by the patient's diary.

Blood pressure load is the percentage of all systolic and diastolic BP recordings exceeding the threshold of 140/90 mmHg^[8]. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Mean blood pressure was calculated as diastolic blood pressure plus one third pulse pressure^[8].

Treadmill exercise ECG test protocol:

All patients in the study underwent the exercise ECG test using standard or modified Bruce models. Resting blood pressure (measured manually by arm-cuff sphygmomanometer) was measured in supine and standing positions before the test. Patients with orthostatic hypotension (defined as a decrease of > 20 mmHg of systolic blood pressure after standing) were excluded. Resting ECG was done for all patients to exclude patients with significant ST-segment changes, left bundle branch block or tachyarrhythmias. Blood pressure was recorded midway through each stage and at peak exercise.

The stress ECG test was terminated if there was a decrease in blood pressure (> 20 mmHg), significant arrhythmias (non-sustained or sustained ventricular tachycardia), typical chest pain (test limiting angina) or > 2 mm ST-segment depression from baseline was noted^[9]. Peak heart rate (HR): achieved percentage of age - related peak heart rate = (peak HR/220 - age) x 100.

Design of the study:

All patients and normotensive control subjects were informed about the study protocol. They underwent identical study protocol, transthoracic echocardiography and blood pressure measurement at rest and after hand-grip isometric exercise.

Assessment of aortic root compliance:

In order to assess aortic root compliance (C), aortic root area (A) was calculated from each measured aortic root dimension (D), assuming the

aorta to be a cylinder with formula: $A = D^2/4$.

Aortic root area (A) was normalized for body surface area in order to account for individual variability related to body size.

Aortic root compliance (C) can be defined by $C = A/P$ ($\text{cm}^2/\text{m}^2/\text{mmHg}$). Where A is the variation of aortic root area index between measurements at rest and during isometric exercise and P is the variation of pressure between measurements at rest and after isometric exercise^[10].

Echocardiographic study:

Two-dimensional and M-mode echocardiography was performed for all patients in the study using Toshiba Power Vision and a 3.5 MHz phased array transducer. Measurements were performed according to the recommendations of the American Society of Cardiology^[11]. The leading edge to leading edge convention was used. Left ventricular dimensions were measured at or immediately below the tips of mitral leaflets and averaged over five heart cycles. Left Ventricular Mass (LVM) and LVM index were calculated. Aortic measurements were determined at end-systole and end diastole from the leading edge of anterior wall of aorta to the leading edge of the posterior wall of aorta.

Hand Grip Isometric Exercise:

In order to provide aortic measurements over a range of pressures, all subjects performed isometric exercise. They were asked to resist inflation of a cuff of sphygmomanometer while aortic dimensions and blood pressure were obtained after three minutes at 50% of maximal hand grip^[10].

Statistical analysis:

Continuous variables are summarized as a mean \pm standard deviation (SD). Comparison between two groups was performed with t - test for continuous variables and chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant and a p-value < 0.01 was considered statistically highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with reduced aortic root compliance in the hypertensive patients. The strength of the association with reduced aortic compliance is presented as 95% confidence intervals. Potential confounding of clinical variables was entered as independent variables.

The validity of the aortic root compliance to detect coronary artery disease and ischemic heart disease was assessed by estimating the predictive indices and Kappa coefficient to determine the overall agreement with the data obtained from the coronary angiography and the treadmill exercise ECG test.

Kappa coefficient value (k) = (Observed frequency of agreement - Expected frequency of agreement) / (Total observed - Expected frequency of agreement).

Predictive indices:

True positive (TP), true negative (TN), false positive (FP) and false negative (FN) were calculated. Sensitivity = $TP / (TP + FN)$, specificity = $TN / (TN + FP)$, positive predictive value = $TP / (TP + TN)$, negative predictive value = $TN / (TN + FP)$ and accuracy = $(TP + TN) / (TP + TN + FP + FN)$.

Simple linear regression (Least-square method) was used for correlation of the aortic root compliance and the systolic blood pressure load: $Y = b + aX$ where, a = slope of the curve and b = intercept of Y dependent axis (aortic root compliance) when X independent value (systolic blood pressure load) became zero.

RESULTS

Clinical characteristics:

As regards the age and gender, there was no significant difference between both groups in the study (54.21 ± 7.24 versus 49.9 ± 4.41 years, respectively, p = NS, 120 (85.7%) versus 25 (83%) males, p = NS and 20 (14.3%) versus 5 (17%) females, p = NS) respectively.

There was no significant difference between both groups regarding a percentage of patients with history of smoking, diabetes mellitus, and hypercholesterolemia [46 (32.7%) versus 12 (40%) patients, p = NS, 29 (20.7%) versus 7 (23%) and 42 (30%) versus 8 (27%) patients, p = NS] respectively. There was no significant difference regarding the resting heart rate between both groups (89.25 ± 5.93 versus 78.5 ± 8.72 beat/minute, respectively, p = NS) but there was a significant increase in the systolic and diastolic blood pressure in the hypertensive patients than the normotensives (177.5 ± 13.41 versus 122.35 ± 8.11 mmHg, and 105.8 ± 5.32 versus 76.84 ± 6.18 mmHg, respectively, p < 0.05).

There were 46 patients with a history of antihypertensive medication with angiotensin converting enzyme inhibitors, 32 patients were on calcium channel blockers, 35 patients were taking beta-blockers and 27 patients were on angiotensin receptors blockers.

Exercise ECG test:

There was no significant difference between both groups in the study as regards the duration of exercise ECG test, peak heart rate, blood pressure response during and after exercise and heart rate recovery after exercise during recovery (p = NS). There was a significant increased ST - segment

Table 1: Aortic root dimensions before and after isometric exercise detected by M-mode echocardiography in both study groups

Variables	Group I	Group II	p-value
At rest before isometric exercise			
Aortic Root Area (cm ²)	8.10 ± 1.32	7.26 ± 1.28	< 0.05
Aortic root Index (cm ² /m ²)	4.34 ± 0.58	3.82 ± 0.64	< 0.05
After 3-minutes hand-grip isometric exercise			
Aortic Root Area (cm ²)	8.99 ± 1.12	8.64 ± 1.07	NS
Aortic Root Index (cm ² /m ²)	4.64 ± 0.36	4.59 ± 0.62	NS

Table 3: Stepwise Logistic Multivariate Analysis of patients with normal aortic function versus those with impaired aortic function as regards age, gender, smoking and hypercholesterolemia

Variables	Co-efficient	p-value	95% CI
Age	0.4653	< 0.05	1.125 - 4.091
Gender	0.6301	< 0.05	1.021 - 3.505
Smoking Status	0.5873	< 0.05	1.761 - 2.723
Hypercholesterolemia	0.1852	< 0.05	1.420 - 2.795

depression in the hypertensive patients than the normotensive subjects (1.75 ± 0.23 versus 0.42 ± 0.11 mm, respectively, $p < 0.05$).

Echocardiography:

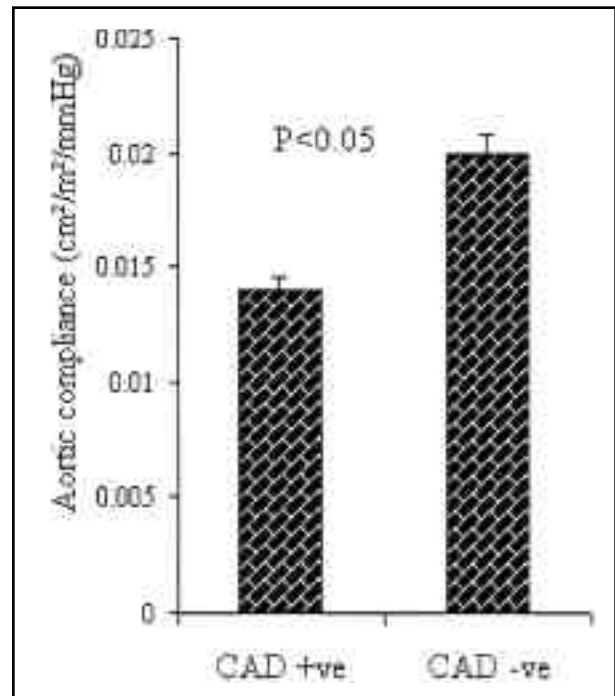
There was a significant increase in the left ventricular mass index (LVMI) in both hypertensive patients and normotensive subjects (147.3 ± 5.32 versus 119.4 ± 4.68 gm/m², $p < 0.05$). There was non-significant difference in the left ventricular systolic function (EF%) between both groups (62.53 ± 4.26 versus $63.41 \pm 2.18\%$, $p = NS$), but there was a significant impaired diastolic function of the left ventricle in the hypertensives than normotensives as there was a significant decrease in the E/A ratio (0.88 ± 0.15 versus 1.51 ± 0.16 respectively, $p < 0.05$). There was no patient with signs of aortic root dissection and there were 20 patients with aortic sclerosis and the mean of the left ventricle/aorta gradient was 24 mmHg. There was no patient with intramural thrombus or pericardial effusion.

There was a significant increase in the aortic root area and the aortic root area index at baseline before isometric exercise in hypertensive patients than normotensive subjects (8.10 ± 1.32 versus 7.26 ± 1.28 cm², $p < 0.05$ and 4.34 ± 0.58 versus 3.82 ± 0.64 cm²/m², $p < 0.05$, respectively), but no significant change in the aortic root area and aortic root area index after isometric exercise between both groups in the study (8.99 ± 1.12 versus 8.64 ± 1.07 cm², $p = NS$ and 4.64 ± 0.36 versus 4.59 ± 0.62 cm²/m², $p = NS$, Table 1).

Table 2: Compliance of the aortic root in both groups

Variables	Group I	Group II	p-value
A (cm ² /m ²)	0.89 ± 0.08	1.38 ± 0.18	< 0.05
P (mmHg)	36.1 ± 4.61	26.4 ± 3.27	< 0.05
C (cm ² /m ² /mmHg)	0.025±0.005	0.052±0.009	< 0.01

C = compliance, A= difference in aortic area, P= difference in systolic blood pressure

**Fig. 1:** Aortic root compliance in the patients with and those without coronary artery disease

There was a significant increase in the aortic area after isometric exercise in the normotensive subjects than before exercise ($p < 0.05$) but no significant increase after exercise in the hypertensive patients ($p = NS$).

There was a significant decrease in the aortic root compliance in hypertensive patients than normotensive subjects (0.025 ± 0.005 versus 0.052 ± 0.009 cm²/m²/mmHg, $p < 0.01$, Table 2).

There was a significant decrease in the aortic root compliance in hypertensive patients with coronary artery disease than those with normal coronary arteries ($p < 0.05$, Fig. 1).

Blood pressure load:

Forty-five hypertensive patients had systolic blood pressure load $> 50\%$ and 55 hypertensive patients had systolic blood pressure load $< 50\%$.

Stepwise logistic multivariate analysis revealed a significant relation between age, gender, smoking status and hypercholesterolemia as independent variables and reduced aortic root compliance in the hypertensive patients ($r = 0.4653, 0.6301, 0.5873$ and 0.1852 and $95\% CI = 1.125 - 4.091, 1.021 - 3.505,$

Table 4: Stepwise Logistic Multivariate Analysis of patients with normal aortic function versus those with impaired aortic function as regards antihypertensive drugs

Variables	Co-efficient	p-value	95% CI
Beta blockers	0.1653	NS	0.524 - 1.091
ACE inhibitors	0.4341	< 0.05	1.227 - 2.893
AR Blockers	0.3821	NS	0.761 - 1.590
Calcium channel blockers	0.1659	<0.05	1.428 - 3.236

ACE = angiotensin converting enzyme, AR = angiotensin receptors

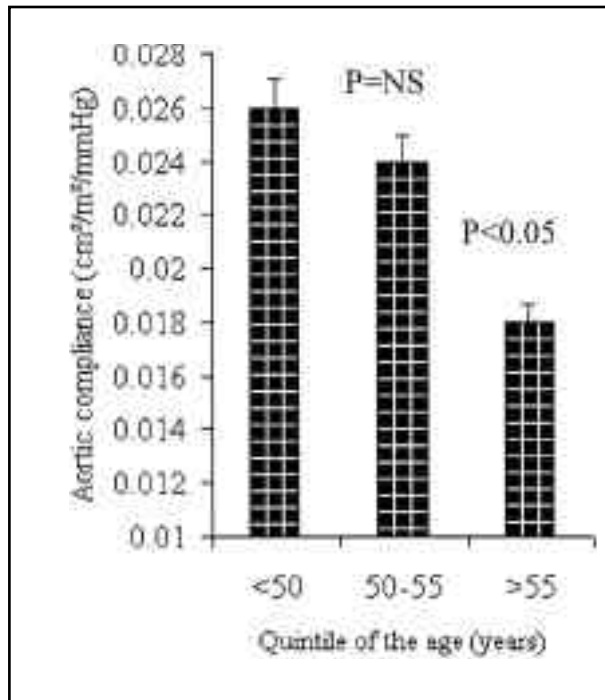


Fig. 2: The aortic root compliance among the three quintiles of the hypertensive patients

1.761 - 2.723 and 1.420 - 2.795, respectively, $p < 0.05$, Table 3). As regards antihypertensive drugs, there was a significant relation between ACE inhibitors and calcium channel blockers as independent variables and a reduced aortic root stiffness in hypertensive patients ($R = 0.4341$ & 0.1659 and $95\%CI = 1.227 - 2.893$ & $1.428 - 3.326$ respectively, $p < 0.05$), but there was no significant relationship between beta blockers and angiotensin receptors blockers as independent variables and a reduced aortic root stiffness in the same group ($r = 0.1653$ & 0.3821 and $95\%CI = 0.524 - 1.091$ & $0.761 - 1.590$ respectively, $p = NS$, Table 4).

Among the quintiles of the age of hypertensive patients there was an insignificant difference regarding the aortic root compliance between the first and second quintiles ($p = NS$), but there was a significant decrease in the aortic root compliance in the third quintile as compared with the first and the second quintiles ($p < 0.5$, Fig. 2).

There was an agreement between data of aortic root compliance and the treadmill exercise ECG test

Table 5: Agreement of the treadmill exercise ECG test and aortic root compliance as regards the prediction of ischemic heart disease

	TTT +ve	TTT -ve	
Stiff aortic root	30	35	65
Compliant aorta	20	55	75
Total	50	90	140

Kappa Co-efficient value (k) = 0.635

TTT = treadmill tolerance test

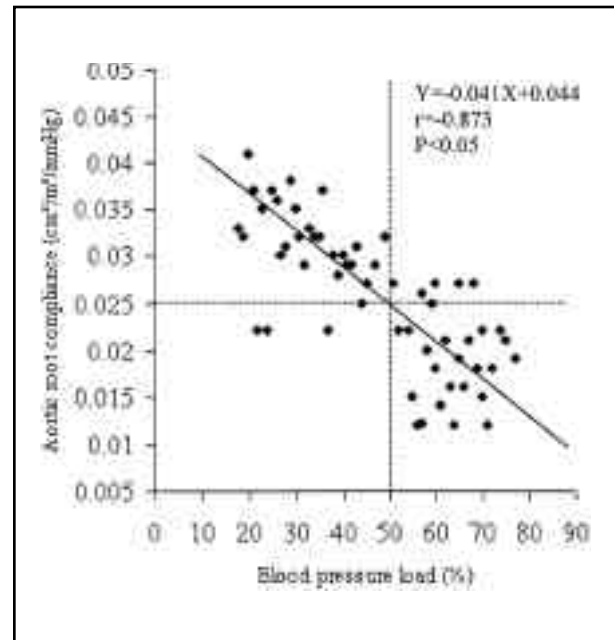


Fig. 3: Correlation between blood pressure load and aortic root compliance in the hypertensive patients

to predict the associated ischemic heart disease with Kappa coefficient value (K) = 0.635, (Table 5) and with the data of coronary angiography to predict the associated coronary artery disease with Kappa coefficient value (K) = 0.761 (Table 6).

There was a significant correlation between blood pressure load (%) and aortic root compliance (cm²/m²/mmHg) in hypertensive patients ($Y = -0.041X + 0.044$, $r = -0.873$, $p < 0.05$), and the aortic root compliance (0.025 cm²/m²/mmHg) of dependent Y axis corresponded with the blood pressure load (50%) of independent X axis (Fig. 3).

Table 7 shows the predictive indices for prediction of the patients with coronary artery disease and to predict the ischemic heart disease.

DISCUSSION

Stefanadis *et al*^[12] reported that aortic stiffness and energy loss due to wall viscosity are increased in hypertensive as compared to the normotensive patients and diltiazem administration produced an acute improvement of aortic elastic properties and a reduction of viscous energy loss. Analysis of the pressure - diameter relation loop provides a

Table 6: Agreement of the coronary angiography and aortic root compliance as regards the prediction of coronary artery disease

	Angio +ve	Angio -ve	
Stiff aortic root	45	10	55
Compliant aorta	20	25	45
Total	65	35	100

Kappa Coefficient value (k) = 0.761

Angio = coronary angiography

valuable insight into aortic mechanics. First, indices such as distensibility and slope of the pressure-diameter loop may be calculated. Second, a study of the pressure-diameter relationship helps distinguish between active and passive changes in aortic elastic properties. The pressure-diameter relationship for a given subject has a sigmoid configuration. Movement of the pressure-diameter loop along this hypothetical sigmoid line suggests changes in the elastic properties of the aorta due to changes in aortic pressure alone. In contrast, shifting of essential modification of the intrinsic properties of the aorta is also due to non-passive factors^[13]. Third, study of the pressure-diameter loop provides insights into aortic energetics. In specific, the area within the loop represents the energy dissipated to the viscosity of the aortic wall.

Several studies suggest that in hypertension, the aorta exposed to increased intraluminal pressure undergoes an increase in mural thickness^[14]. Moreover, changes in the structural components of the arterial wall, including a fall in the ratio of elastin to collagen, may account for stiffening of the aorta^[15]. In addition, increased smooth muscle tension is a possible contributor to aortic wall stiffening in hypertension. Hypertension-induced endothelial cell dysfunction may also contribute to alterations of the arterial wall tone, most likely through impairment of nitric oxide-mediated vascular smooth muscle relaxation. In advanced stages of the disease, a further factor that reduces arterial compliance is the deposition of calcium^[16].

The amount of severity of atherosclerosis in the coronary bed shows a positive correlation with the degree of atherosclerosis in the aorta or other major arterial branches^[17]. Atherosclerotic changes in arterial wall have been shown to include smooth muscle cell proliferation, deposition of lipid and accumulation of collagen, elastin and proteoglycans. Changes in the ratio of collagen to elastin have been known to structurally affect the elastic behavior of arterial walls.

Our finding of an impaired aortic root compliance in hypertensive patients with coronary artery

Table 7: Indices for prediction of coronary artery disease by echocardiographic assessment of aortic root compliance in all patients group

	TP	TN	FP	FN	Sen	Spec	Acc	PPV	NPV
Prediction of IHD	30	55	35	20	60%	67%	60%	46%	73%
Prediction of CAD	45	25	10	20	69%	71%	70%	81%	56%

TP= true positive, TN = true negative, FN = false negative, FP= false positive, Sen = sensitivity, Spec = specificity, Acc = accuracy, PPV = positive predictive value, NPV = negative predictive value

disease is in keeping with previous smaller studies^[18]. Another study has shown that proximal aortic stiffness is increased progressively with the number of diseased coronary blood vessels in patients investigated after myocardial infarction^[19]. Only 100 patients were known to have undergone coronary angiography in the course of their routine clinical management and out of these only 40 patients had normal coronary arteriography, 10 patients had positive exercise test which may be due to other causes (e.g., coronary spasm or microvascular disease), and this seems unlikely to have seriously confounded our results.

We found that the age, gender, smoking status and hypercholesterolemia were independent variables to increase the risk of the aortic stiffness and this is in an agreement with other studies^[19-22]. An increase in the stiffness of the aorta with elevated plasma lipids has been related to the increased endothelium vasoactivity and decreased vasa vasorum flow. Cholesterol may enhance arterial stiffening, but this process is modulated by other risk factors for CAD^[20].

Smoking is a major and independent risk factor for cardiovascular morbidity and mortality^[21]. Many underlying mechanisms have been proposed for the hazardous effects of smoking, including promotion of atherogenesis, unfavourably changed lipid profile, increased blood viscosity, alterations in platelet function and promotion of thrombosis and enhanced adrenergic activity. Previous studies have shown that smoking also induces coronary artery vasoconstriction and affects arterial elastic properties unfavorably, increasing stiffness of both muscular and elastic arteries.

We found that the angiotensin converting enzyme inhibitors and calcium channel blockers were independent variables for decreasing the risk of the aortic stiffness and this is in agreement with other studies^[23,24]. Diltiazem has an active effect on the elastic properties of the aorta due to direct relaxation of the aortic smooth muscle and increase in the vasodilatory capacity of the vasa vasorum of the aortic wall which is decreased in chronic hypertension^[3].

Methodological consideration:

The method used in the present study provides reliable, non-invasive and valid determination of the aortic root function in hypertensive patients and can be reproduced in the hypertension clinic but the invasive methods using the high fidelity diameter measuring device and the catheter-tip micromanometer measuring aortic pressure has been validated and proved to be accurate and safe^[3]. The variability of echocardiography determined indices of aortic stiffness has been found previously to be < 10% for inter-observer comparisons. For measurements repeated at 4-week intervals, intra-observer variability was < 10%^[3,17]. In our study only one cardiologist performed echocardiographic assessment once. Therefore it is difficult to assess inter-observer and intra-observer variability.

Limitations of the study:

1. Relatively small number of patients.
2. The study was not blind to the cardiologist performing the echocardiography.
3. Blood pressure was recorded indirectly by cuff sphygmomanometer.
4. Coronary vasomotor reactivity was not included in the design of the study.
5. Pregnant women were not included in the study to avoid the confounding effect of the estrogen on the elasticity of the aorta. The aorta is more dilated and more compliant during normal human pregnancy, especially in multi-parus women^[25].
6. Hypertensive patients with end-organ damage were not included in the study.

CONCLUSION

Aortic root compliance is compromised in hypertensive patients as compared with normotensive subjects and it can be considered as a marker for prediction of coronary artery disease. Aortic root compliance is a precise estimate for risk stratification in the management of hypertensive patients as the serial evaluation of the aortic root stiffness allows early detection of pathologic acceleration of atherosclerotic complications.

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