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Original Article

Association between coronary artery disease and responsiveness of aortic stiffness and pulsatile diameter change to nitroglycerin

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Abstract

Aim: This study aimed to evaluate the difference between the effect of nitroglycerin on the aortic stiffness measured by transthoracic M-mode ultrasonography in patients with and without coronary artery disease (CAD).
Material and Methods: This study was conducted on one hundredpatients with a presume diagnosis of CAD. The patients who had a SYNTAX score (SS) ≥1 according to the results of coronary angiography constituted the CAD group (n:60), while patients who had a SS=0 constituted the control group (n:40).The stiffness of the ascending aorta and arterial blood pressure were measured before and 10 minutes after the sublingual administration of 800 mcg nitroglycerin. A comparison of each parameter before and after nitroglycerin was evaluated for statistical significance using paired sample t-test.
Results: In the control group, after nitroglycerin administration, there was a statistically significant reduction in the pulsatile diameter change (from 2.30±0.79 to 1.74±0.91) and significant increase in stiffness index (from 6.24±2.41 to 9.07±5.88). In the CAD group, after nitroglycerin administration, there wasno statistically significant difference in terms of pulsatile diameter change (from 1.42±0.88 to 1.28±0.68) and stiffness index (from 13.52±7.64 to 13.10±7.85).
Conclusion: The effect of nitroglycerin on the aortic stiffness measured by transthoracic M-mode ultrasonography differs in the CAD and control groups. Our findings warrant further studies with a larger population to describe the practicability of this method for the CAD diagnosis.

Keywords: Aorta; Coronary Artery Disease; Stiffness; Nitroglycerin.

INTRODUCTION

The stiffness of the aortamay cause an abnormal pressure pattern that increases the afterload of the left ventricle. In that way, it may induce a left ventricular hypertrophy, left ventricular diastolic and systolic dysfunction as well as coronary ischemia. It is a well-knownthat theaortic stiffness is an independent predictor of all cause-mortality in different groups of patients (1).

Several previous studies demonstrated that the elasticity of the ascending aorta decreases in the presence of coronary artery disease (CAD) (2,3). For example, the blood flow to the vasa-vasorum of the ascending aorta decreasesin patients with CAD because the blood vessels that supply the vaso-vasorum of the ascending aorta originate from the coronary arteries (4). Moreover, similar grades of atherosclerosis, which was found an autopsy analysis of patients, develop on the distribution of coronary and aortic atherosclerosis. Consequently, atherosclerosis may affect the aortic elasticity (5,6). The decreased aortic elasticity causes an increase ofthe central pulsatile pressure, therebyresults inanincreased vessel wall tension. The increased vessel wall tension eventually leads to atherosclerosis by causing endothelial dysfunction (7).

Nitroglycerin may increase distensibility of peripheral muscular arteries (8). However, the effect of nitroglycerin

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onthestiffness of aorta, as an elastic artery, has not been precisely clarified. There is also a conflictingdata about the impact of nitroglycerin on theaortic stiffness in the presence of CAD. Shimizu et al. reported a reduction inthe arterial stiffness, measured by cardio-ankle vascular index,in healthy subjects and patients with CAD after nitroglycerin administration (9). On the other hand, Yamamoto et al. demonstrated that after nitroglycerin administration, there was only a decreased of the aortic stiffness in healthy subjects in contrast to CAD patients (10).

The aim of the study was to evaluate the difference between effects of nitroglycerin on the aortic stiffness measured by transthoracic M-mode ultrasonography in patients with and without CAD.

MATERIAL and METHODS

Patient selection and study protocol

This study was conducted on the patients admitted for elective coronary angiography with a presume diagnosis of CAD. In the present study, all patients underwent a coronary angiography. The patients who had SYNTAX score (SS) ≥1 according to the results of coronary angiography constituted the CAD group, while the patients who had a SS=0 constituted the control group.The stiffness of the ascending aorta and arterial blood pressure were measured before and 10 min after the sublingual administration of 800 mcg nitroglycerin. A detailed clinical history, including cardiovascular risk factors and all medication was obtained from all participants. In the study, all patients continued to their medications.

The patients who had at least one of the following factors were excluded from the study. These were;hemodynamic instability, cerebrovascular incident, severe valvularheartdisease, heart failure (ejection fraction (EF) of <45%), chronicrenal failure, atrial fibrillation, any aortic vessel disease such as aortic aneurysm, Marfan syndrome, aorticcoarctation, and a previous aortic valve surgery, a prior revascularization such as percutaneouscoronary angioplasty or coronary aortic by-pass surgery, a previous history of myocardial infarction. In addition, the patients whose echocardiographic image quality was insufficient were excluded from the study.

The patients' baseline demographic characteristics and all medications including age, gender, height, weight, hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, calcium channel blocker, and nitrate use were recorded. The body mass index (BMI) was calculated for aneach patient using a following equation; weight divided by height squared (kg/m2). The patients were considered to have diabetes mellitus if their fasting blood sugar levels ≥ 126mg/dL or used oral hypoglycemic agents, insulin sensitizers, or insulin. Hypertension was defined as systolic blood pressure (SBP) ≥ 140mmHg or diastolic blood pressure (DBP) ≥ 90mmHg, or self-reported use of antihypertensive medication. The criterion for hyperlipidemia was total cholesterol level ≥220 mg/dl or receiving a lipid-lowering therapy.

Each subject provided an informed written consent prior to participate in the study. The study was approved by our university Ethics review board, and it was conducted in accordance with the principles of the Declaration of Helsinki.

Blood pressure measurement

Blood pressure was measured using sphygmomanometer with a standard cuff from the right arm. The echocardiographic examination was simultaneously performed during the blood pressure monitoring. The first and fifth Korotkoff sounds were accepted as systolic and diastolic blood pressure values, respectively. The pulse pressure (PP) and the mean blood pressure (MBP) were calculated using the following formulas;

PP = SBP – DBP

MBP= (2 x DBP + SBP) / 3

Echocardiographic examination

Transthoracic echocardiography was performed using 3.5 MHzphasedprobewithaPhilipsHD11XEdeviceatthelateral decubitus position.A continuous electrocardiography (ECG) monitoring was performedduring the procedure. M-mode and 2D measurements were performed on the parasternal long axis view in accordance with guidelines of American Society of Echocardiography. The left ventricle EF was calculated with using the Teichholz method (11,12). Afteranobserving the ascending aorta on the parasternal long-axis, M-mode transducer was placed passing through the ascending aorta region at 3 cm distal to the aortic valve in order to obtain the trace for calculation of systolic and diastolic diameters of the ascending aorta (Figure 1) (13,14). A systolic diameter was measured from themaximumpoint of forward motion in the aortic trace, whilea diastolic diameter was measured from the locationaccording to the Rwave peak on the ECG. The mean systolic and diastolic measurements were calculated from a three consecutive measurements. The aortic elasticity parameters such as stiffness index (SI) and aortic dispensability (AD) were calculated using the following formulas (13,14).

Systolic diameter – diastolic diameter = pulsatile diameter change

SI= ln (SBP/DBP) / (pulsatile diameter change)/ diastolic diameter)

AD (cm2.dyn-1.10-6)=2x (pulsatile diameter change)/ PP x diastolic diameter

All echocardiography were performed and analyzed by one cardiologist who was blinded to clinic data of the patient. Intra-observer variability was calculated as the difference in two measurements of the same patient by one observer divided by the mean value. Intra-observer variability's were less than 5% for aortic elasticity measurements.

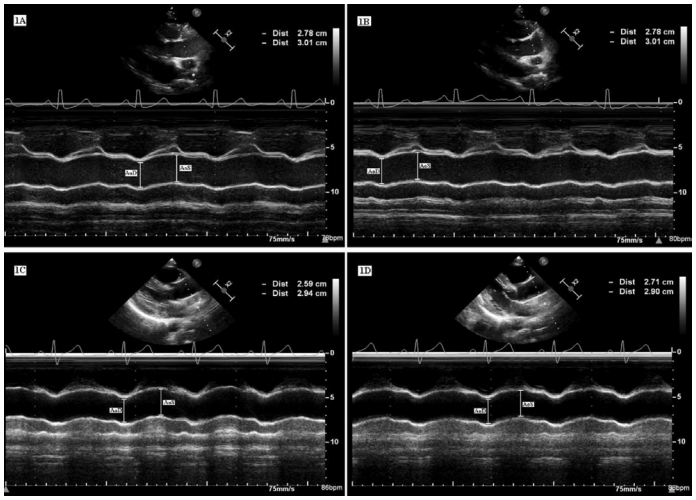

Figure 1. Systolic and diastolic diameter measurements of the ascending aorta with M-mode echocardiography. Before (1A) and after (1B) sublingual administration of nitroglycerin, there was no change in pulsatile diameter change in a CAD patient. Before (1C) and after (1D) sublingual administration of nitroglycerin, there was a prominent decrease in pulsatile diameter change in a non-CAD patient after nitroglycerin. AoS: Aortic systolic diameter, AoD: Aortic diastolic diameter

Angiographic evaluation

All patients underwent a selective coronary angiography using the Judkins percutaneous trans-femoral technique. Coronary angiograms were recorded in digital media for quantitative analysis (Dicom-viewer; MedCom GmbH, Darmstadt, Germany). Coronary angiograms were analyzed by two independent interventional cardiologists, who were blinded to patients' data. The CAD was classifiedaccording to SYNTAX scoring. Each lesion ≥1.5 mm in diameter and with ≥50% stenosis was scored and the total score of each patient was calculated using the online SYNTAX score Calculator, version 2.1 (www.syntaxscore.com). Patients with SS ≥1 were considered to have CAD, whilethose with SS=0 were considered as control group.

Statistical analysis

The definitive statistics was separately performed for the samples in the CAD and control groups for the presentation of the demographic characteristics of the study group. The mean value±standard deviation was used for continuous variables. The frequencies and percentages (%) were used for a categorical data.The Chi-square test was used to determine whether there was a difference between the groups with respect to the variables such as gender, hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, angiotensin receptor blocker, beta blocker, calcium channel blocker, and nitrate. Independent sample t-test was used to determine whether there was a difference between the groups with respect to the variables such as weight, height, BMI, EF, age, aortic elasticity parameters, blood pressure and heart rate. Paired sample t-test was used for acomparison between the results obtained before and after nitroglycerin administration. The correlation of the Δ stiffness index and the Δ pulsatile diameter change with SS was assessed using Pearson correlation analyses. The Δ stiffness index and the Δ pulsatile diameter change with the best specificity and sensitivity for predicting presence of CAD was calculated using receiver-operating characteristic (ROC) curve analysis. Statistical analyses were performed using SPSS v.11.5 and Med Calc v11.0 package software. A statistical significance level was accepted as $p<0.05$.

The effect size (Cohen's d) and power value (1-β) of the stiffness index and thepulsatile diameter change comparison between patients with and without CAD were calculated using G*Power software (version 3.1.9.2). The alpha level used for this analysis was < 0.05. The effect size and power value of the stiffness index comparison were 1.28 and 0.95, respectively, and the effect size and power value of the pulsatile diameter change comparison were 1.05 and 0.95, respectively.The mean stiffness index of patients with and without CAD was 13.5 ± 7.6 and 6.2 ± 2.4, respectively. The minimum number of patients to be enrolled in this study was calculated, and it was found to be 13 for those with CAD and 13 for those without CAD. The mean pulsatile diameter change average of patients with and without CAD was 1.4± 0.9 and 2.3± 0.8, respectively. The minimum number of patients to be enrolled in this study was calculated, and it was foundto be 21 for those with CAD and 21 for those without CAD.

RESULTS

According to the results of coronary angiography, 60 subjects who had a SS≥1 constituted the CAD group, while 40 subjects who had aSS=0 constituted the control group. The groups were similar in terms of baseline demographic characteristics excluding age, gender, aortic distensibility, pulsatile diameter change and stiffness index ($p<0.05$, for all) (Table 1).

In the CAD group, a comparison between the hemodynamic and aortic characteristics before and after administration of nitroglycerin demonstrated a statistically significant reduction inthe systolic blood pressure, the mean blood pressure, andthe pulse pressure ($p<0.05$, for all). A reduction in the diastolic blood pressure was also statistically significant between both groups ($p=0.045$). In addition, the increase of heart rate was statistically significantbetween both groups ($p<0.001$) (Table 2). There was no statistically significant difference in terms of apulsatile diameter change, aortic distensibility, and stiffness index (Table 2).

In the control group, acomparison between the hemodynamic and aortic characteristics before and after administration of nitroglycerin showeda statistically significant reduction in systolic blood pressure, mean blood pressure and pulse pressure ($p<0.05$, for all). Areduction in diastolic blood pressure was also statistically significantbetween both groups ($p=0.047$). The increase of heart rate was statistically significant between both groups($p=0.001$) (Table 2). There was a statistically significant reduction in pulsatile diameter change andasignificant increase in thestiffness index ($p<0.001$ and $p<0.001$, respectively). There was no statistically significant difference in terms of aortic distensibility between both groups (Table 2).

Bothgroups were similar with respect to the pressure and heart rate changes after nitroglycerin administration (p>0.05 for all). In terms of the aortic elasticity parameters, the stiffness index was found to be a statistically significant (p=0.024), while the aortic distensibility was statistically insignificant after nitroglycerin administration (Table 2). There was also a statistically significant difference in terms of pulsatile diameter change after nitroglycerin administration between the groups (p=0.014) (Table 2).

In the receiver operating characteristic (ROC) curve analysis, the area under curve (AUC) of the Δ stiffness index was 0.690 (95% CI: 0.590–0.779, p<0.001). Theoptimal cut-off value for the Δ stiffness index that indicated a CAD was ≤-0.667 with 55% sensitivity and 82.5% specificity (Figure 2).

Similarly, the AUC of the Δ pulsatile diameter change was 0.666 (95% CI: 0.564–0.757, p=0.007). Theoptimal cut-off value for the Δ pulsatile diameter change that indicated a CAD was >-0.03 with 70% sensitivity and 70% specificity (Figure 3).

In acorrelation analyses, there was a moderate inverse correlation between the Δ stiffness index and the SS (r= -0.475, p<0.001), and a weak-moderate correlation between the Δ pulsatile diameter change and the SS (r=0.327, p=0.011) (Table 3).

Table1. Demographic and definitive characteristics of the groups

	Total cohort (n=100)	Control group (n=40)	CAD group (n=60)	p
Male n (%)	55 (55.0%)	15 (37.5%)	40 (66.7%)	0.004
Body mass index (kg/m2)	27.71±3.83	27.92±4.22	27.58±3.57	0.668
LVEF (%)	60.38±9.96	61.23±8.38	59.82±10.91	0.491
Age (years)	57.51±10.57	53.78±10.00	60.00±10.28	0.003
Hypertension n (%)	51 (51.0%)	19 (47.5%)	32 (53.3%)	0.568
Diabetes mellitus n (%)	24 (24.0%)	9 (22.5%)	15 (25%)	0.774
Hyperlipidemia n (%)	41 (41.0%)	19 (47.5%)	22 (36.7%)	0.281
Cigarette smoking n (%)	30 (30.0%)	9 (22.5%)	21 (35%)	0.181
ARB use n (%)	13 (13.0%)	6 (15%)	7 (11.7%)	0.627
ACEI use n (%)	21 (21.0%)	8 (20%)	13 (21.7%)	0.84
Beta blocker use n (%)	24 (24.0%)	8 (20%)	16 (26.7%)	0.444
CCB use n (%)	10 (10.0%)	2 (5%)	8 (13.3%)	0.156
Nitrate use n (%)	10 (10.0%)	4 (10%)	6 (10%)	1.000
SBP (mmHg)	124.40±16.94	123.75±18.04	124.88±16.31	0.756
DBP (mmHg)	77.15±11.22	78.50±11.99	76.25±10.68	0.328
Pulse pressure (mmHg)	47.25±10.62	45.25±10.74	48.58±10.42	0.125
Pulsatile diameter change (mm)	1.77±0.95	2.30±0.79	1.42±0.88	<0.001
Aortic distensibility (cm2.dyn-1.10-6)	2.10±1.37	2.86±1.28	1.59±1.20	<0.001
Stiffness index	10.61±7.06	6.24±2.41	13.52±7.64	<0.001
Heart Rate (beats/min)	67.09±11.23	65.82±11.22	67.93±11.25	0.360
MBP(mmHg)	92.90±12.43	93.58±13.37	92.44±11.86	0.656
SYNTAX Score	-	-	18.8±8.6	

Abbreviations: ACEI- angiotensin converting enzyme inhibitör; ARB- angiotensin receptor blocker; CCB- calcium channel blocker; CAD- coronary artery disease; DBP- diastolic blood pressure; LVEF- left ventricular ejection fraction; MBP- mean blood pressure; SBP- systolic blood pressure

Table 2. Hemodynamic and aortic characteristics of the groups before and after nitroglycerin administration

	CAD group (n=60)	CAD group (n=60) after NTG	p-value for CAD group before and after NTG	Control group (n=40)	Control group (n=40) after NTG	p-value for Control group before and after NTG	p-value for Δ changes of variables between groups
SBP (mmHg)	124.83±16.31	114.08±0.35	<0.001	123.75±18.04	113.00±12.70	<0.001	1
DBP (mmHg)	76.25±10.68	74.08±10.68	0.045	78.50±11.99	75.88±9.05	0.047	0.784
Pulsatile diameter change (mm)	1.42±0.88	1.28±0.68	0.134	2.30±0.79	1.74±0.91	<0.001	0.014
Aortic distensibility (cm2. dyn-1.10-6)	1.59±1.20	1.73±1.07	0.328	2.86±1.28	2.53±1.45	0.183	0.154
Stiffness index	13.52±7.64	13.10±7.85	0.700	6.24±2.41	9.07±5.88	<0.001	0.024
MBP(mmHg)	92.44±11.86	87.42±12.06	<0.001	93.58±13.37	88.25±9.60	0.001	0.882
Heart Rate (beats/min)	67.93±11.25	72.05±11.61	<0.001	65.82±11.22	70.25±11.28	0.001	0.822
Pulse pressure (mmHg)	48.58±10.42	40.00±8.34	<0.001	45.25±10.74	37.12±8.54	<0.001	0.817

Abbreviations: DBP- diastolic blood pressure; MBP- mean blood pressure;NTG- nitroglycerin; SBP- systolic blood pressure. Δ changes: subtraction of before nitroglycerin administration levels from after nitroglycerin administration levels

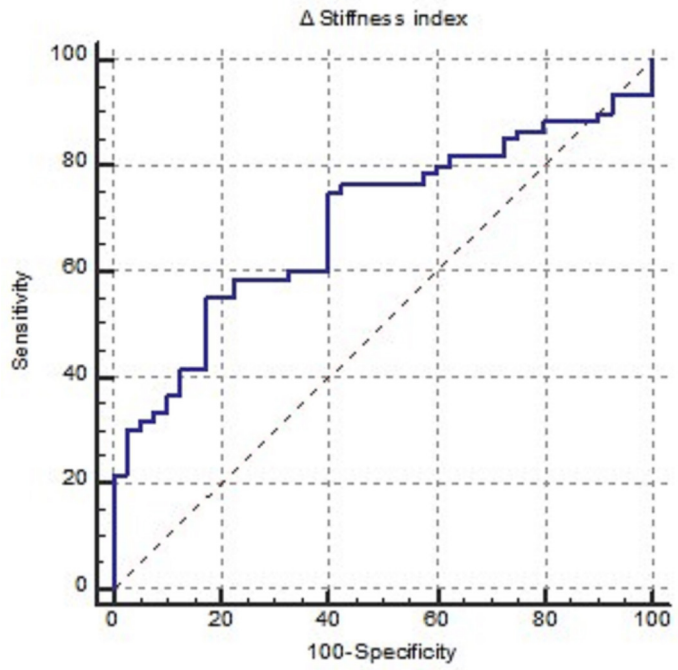

Figure 2. ROC graphic to detect the cut-off value of Δ stiffness index for CAD prediction

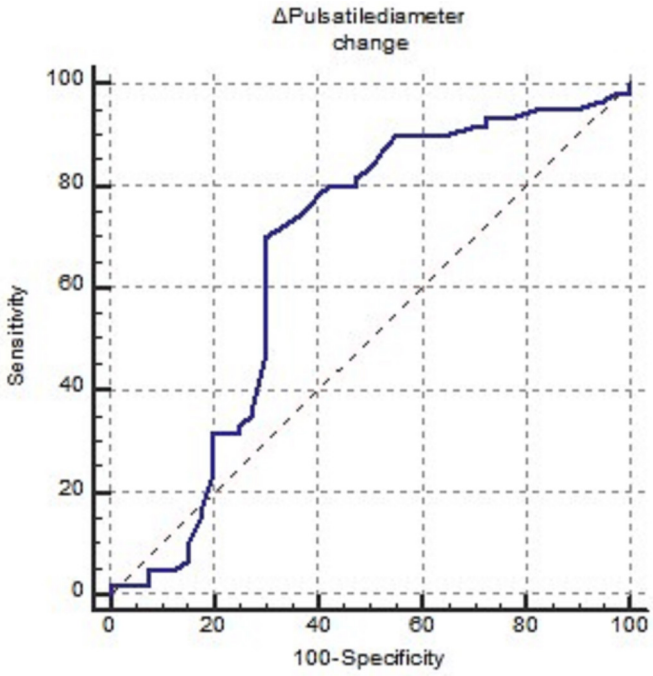

Figure 3. ROC graphic to detect the cut-off value of Δ pulsatile diameter change for CAD prediction

Table 3. Relationship between Δ stiffness index and Δ pulsatile diameter change and SYNTAX score

	SYNTAX score
Δ stiffness index	
r value	-0.475
p value	<0.001
n	60
Δ pulsatile diameter change	
r value	0.327
p value	0.011
n	60

Δ changes: subtractionof before nitroglycerin administration levels from after nitroglycerin administration levels

DISCUSSION

In our study, the presence of CAD was foundto beassociated withthe aortic elasticity parameters such as aortic distensibility and stiffness index. The result of our study is found to be a parallel with a current literature (14-17).

An analysis of the aortic elasticity involves the aorta and its main branches with distinguished characteristics from the smaller and more muscular peripheral arteries such as radial and brachial arteries. The stiffness index and aortic distensibility, which show mechanical features of the aortic wall, are known as aortic elasticity parameters. The aortic elasticity is calculated from a relationship between blood pressure and aortic diameterthat is based on an establishment of an association with the aortic diameter change against the pressure of tensile strength (13).

In our study, after nitroglycerin administration, a significant increase was found in stiffness index in the control group, whereas no differencewas found in the CAD group.There was no statistically significant difference with respect to pulsatile diameter change in CAD group. However, a significant reduction was found in pulsatile diameter change in the control group. The significant increase in stiffness index may be due to the significant reduction in pulsatile diameter change in the control group becausethe control group showed a similar baseline blood pressure level and a similar level of change after nitroglycerin administration. The different effects of pulsatile diameter change onthe aortic distensibility and stiffness index result from their different dependence to blood pressure when a calculation was performed (18). The pulsatile diameter change is affected by pulse pressure, the mean arterial pressure, and absolute aortic elasticity. Because themean arterial pressure is almost same in the central and peripheral arteries, a reduction in this parameter showed a similarincreasing effect on pulsatile diameter change in both groups.The only explanation for the significant difference in terms of pulsatile diameter change between the groups may be a different level of reduction in the central pulse pressure, which could not be perceived in the peripheral pulse because we were only able to measure the blood pressure from the arm. Our study indirectly indicates that nitroglycerin administration leads to a higher reduction in the central pulse pressure in the control group when compared to the CAD group. This issue should be elucidated by further studies with an aim in directmeasuring of the aortic root blood pressure after nitroglycerin administration in those groups.

Nitroglycerin provides a reduction in awave reflection which causes alate systolic pressure peak in the aorta (19). Nitroglycerin has a strong effect on the peripheral muscular arteries with a reduction in wave reflection. Thus, it causesa reduction in the late systolic pressure peak, central systolic blood pressure, and central pulse pressure (19,20). It has been reported that nitroglycerin administration provides a more remarkable reduction in the systolic blood pressure and pulse pressure in the aorta

when compared tothe brachial artery (21,22). It has been alsodemonstrated that vasodilator response of the smooth muscles in the vessel wall to nitroglycerin is impaired in atherosclerosis (23-25). Nitroglycerin may have shown a different grade of effect on the wave reflection in the CAD and control groups because theperipheral muscular arterial dilatation provided by nitroglycerin administration could not be remarkable in the CAD group when compared with the patients in the control group. Even though the results of our study indirectly support the conclusion that nitroglycerin may show different grades of impact on the wave reflection in CAD and control groups, further studies are needed to clarify this issue.

Several limitations of this study should be considered. First, thesample size was small; hence it mayaffect the statistical power of the study. Second,our findings may only be pivotal study for the detection of CAD with a small sample size, that's why definitive conclusions should not be drawn. Third, asthe half of the study patients had hypertension, the effect of medications on the aortic elasticity parameters cannot be excluded. Finally, in our study, the blood pressure was measured using sphygmomanometer as same in a daily life practice because theblood pressure measurement in the ascending aorta usually requires an invasive intervention.

CONCLUSION

Our findings showed that the pulsatile diameter significantly decreased, while the aortic stiffness index significantly increased after nitroglycerin administration in the control group. However, these changes were not encountered in theCAD group.The aortic stiffness measured by transthoracic M-mode ultrasonographyresponse to nitroglycerin differently in the CAD and control groups. Our findings warrant further studies with a larger population to describe the practicability of this method for theCAD diagnosis.

Competing interests: The authors declare that they have no competing interest.
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