Original Research

Chest Pain in Patients with Arterial Hypertension, Angiographically Normal Coronary Arteries and Stiff Aorta: The Aortic Pain Syndrome

Dimitrios A. Stakos[1], Dimitrios N. Tziakas[1], George Chalikias[1], Konstantina Mitrousi[1], Christina Tsigalou[1], Harisios Boudoulas[2,3]

[1]Democritus University of Thrace, Dept. of Cardiology, Greece; [2]The Ohio State University, Columbus, OH, USA; [3]Foundation of Biomedical Research, Academy of Athens, Greece

Key words: **Chest pain, hypertension, stiff aorta, pulse wave velocity, collagen.**

Introduction: Arterial hypertension is often associated with a stiff aorta as a result of collagen accumulation in the aortic wall and may produce chest pain. In the present study, possible interrelationships between aortic function, collagen turnover and exercise-induced chest pain in patients with arterial hypertension and angiographically normal coronary arteries were investigated.

Methods: Ninety-seven patients with arterial hypertension, angiographically normal coronary arteries and no evidence of myocardial ischemia on nuclear cardiac imaging during exercise test were studied. Of these, 43 developed chest pain during exercise (chest pain group) while 54 did not (no chest pain group). Carotid femoral pulse-wave velocity (PWVc-f) was used to assess the elastic properties of the aorta. Amino-terminal pro-peptides of pro-collagen type I, (PINP, reflecting collagen synthesis), serum telopeptides of collagen type I (CITP, reflecting collagen degradation), pro-metalloproteinase 1 (ProMMP-1), and tissue inhibitor of metalloproteinase 1 (TIMP-1, related to collagen turnover) were measured in plasma by immunoassay.

Results: The chest pain group had higher PWVc-f, higher PINP and PINP/CITP ratio, and lower proMMP-1/TIMP-1 ratio compared to the no chest pain group. PWVc-f (t=2.53, p=0.02) and PINP (t=2.42, p=0.02) were independently associated with the presence of chest pain in multiple regression analysis.

Conclusions: Patients with arterial hypertension, exercise-induced chest pain and angiographically normal coronary arteries, without evidence of exercise-induced myocardial ischemia, had a stiffer aorta compared to those without chest pain. Alterations in collagen type I turnover that favor collagen accumulation in the aortic wall may contribute to aortic stiffening and chest pain in these patients.

Manuscript received: November 8, 2011;
Accepted: April 27, 2012.

Address:
Dimitrios A. Stakos

Democritus University of Thrace
Dragana,
681 00 Alexandroupolis
Greece
e-mail: dstakos@med.duth.gr

Exercise-induced chest pain is not uncommon in patients with arterial hypertension, even if they have angiographically normal coronary arteries.[1] Dysfunctional endothelium in the epicardial coronary arteries and impaired myocardial microcirculatory function have both been proposed as important pathophysiological mechanisms.[2-4] However, in patients with normal myocardial perfusion, other causes should be considered. The possibility that the chest pain may be of aortic origin has been suggested but has not been extensively studied.[5-7]

Aortic pain is the leading symptom for catastrophic aortic events, such as dissection, hematoma and penetrating ulcer. Aortic pain, however, may be present in an anatomically normal but functionally abnormal aorta. A stiff aorta is less distensible; thus, an increase in aortic wall tension may occur during exercise, when the central aortic blood pressure suddenly rises.[8] Previous studies have shown that aortic stiffness is associated with alterations

in collagen turnover in patients with arterial hypertension.[9-11]

In this study, we hypothesized that exercise-induced chest pain in patients with arterial hypertension and angiographically normal coronary angiography could be associated with a stiff aorta. The interrelationships among aortic dysfunction, plasma markers of collagen turnover, and chest pain were also investigated.

Methods

Study population

Study participants were selected from the database of the catheterization laboratory of the University Hospital of Alexandroupolis. From January 2008 to December 2009, 3146 patients underwent coronary arteriography, of whom 526 had angiographically normal coronary arteries; 385 of the latter also had arterial hypertension. Patients older than 70 years, those with diabetes mellitus, osteoporosis, left ventricular hypertrophy on the echocardiogram (defined as left ventricular mass >150 g/m^2 for men and >120 g/m^2 for women[12]), more than moderate impairment of left ventricular systolic function (ejection fraction <40%), valvular heart disease, aortic dilatation (defined as ascending aortic diameter >32 mm for men and >28 mm for women[13]) and those who had surgical or percutaneous aortic intervention were excluded from the study.

Participants who met the above criteria underwent an exercise stress test with nuclear imaging in order to assess the possibility of myocardial ischemia. Eighteen individuals did not give informed consent. One hundred five patients had normal nuclear studies without myocardial perfusion defects. Of those, 97 had adequate studies for further analysis: 43 had chest pain during the exercise test while 54 did not. The protocol was approved by the Institutional Review Board for Human Biomedical Research from the University Hospital of Alexandroupolis. Written informed consent was obtained from all participants prior to the study.

Cardiovascular evaluation

History, physical examination and blood pressure measurements were performed in all patients. Brachial artery pressure was measured with subjects in the supine position after they had been seated for at least 5 min. The average of two measurements was used for the analysis.

The exercise stress test was performed using the Bruce protocol, with the patient walking on a treadmill under a workload that gradually increased at 3-minute intervals. Blood pressure was measured manually every 3 minutes during exercise until the test was stopped, and every 3 minutes during the recovery period. At peak exercise, a single dose of intravenous 3 mCi Thallium-201 was injected and images were obtained 3 minutes and 3 hours after the injection. Myocardial perfusion was assessed in the short, vertical and horizontal axis views.

Left ventricular (LV) mass and function were measured by echocardiography using a GE VingMed System 5 device, according to the recommendations of the American Society of Echocardiography.[14,15] The elastic properties of the aorta were assessed in terms of carotid-femoral pulse-wave velocity (PWVcf) using applanation tonometry with a SphygmoCor device (AtCor Medical, Sydney, Australia).[5] Coronary arteriography was performed using the standard Judkins technique. By definition, all patients had angiographically normal coronary arteries.

Indices of collagen synthesis and degradation

Free amino-terminal pro-peptides of pro-collagen type I (PINP) were used as an index of collagen synthesis; serum telopeptides of type I collagen (CITP) were used as an index of collagen degradation; and serum levels of pro-metalloproteinase-1 (ProMMP-1) and its tissue inhibitor TIMP-1 were used as indices of collagen turnover. All measurements were performed using commercially available immunoassay techniques.[9]

Statistical analyses

Statistical analyses were performed using the SPSS (Statistical Package for Social Sciences, Chicago IL, USA) software for Windows (Version 11.0). Results are presented as mean ± 1 standard deviation (SD) for continuous variables and as percentages for categorical data. Normal distribution was tested using the Kolmogorov–Smirnov test. Normally distributed data were compared using Student's t-test. Non-normally distributed data were compared using the Mann–Whitney U-test.

For simple linear correlation analysis, Pearson's correlation coefficient was used. Multiple linear re-

gression analysis was performed using the "backward" deletion method, where significant determinants for the presence of chest pain were entered into the analysis in a single initial step and then variables were removed one at a time, retaining only the statistically significant ones. In another model of multiple linear regression analysis a forced entry was used to analyse the influence of antihypertensive medications on the results. In order to detect possible associations between PWVc-f and different indices of collagen turnover, quartiles of PWVc-f were used and analyzed with ANOVA. A p-value <0.05 was considered statistically significant.

Results

Demographic data and clinical characteristics of the study population are presented in Table 1. Resting hemodynamics and data from the exercise stress test are shown in Table 2. Heart rate and systolic arterial

Table 1. Demographic data and clinical characteristics of the study population.

Parameter	Chest pain n=43	No chest pain n=54	p
Age (years)	62 ± 7	61 ± 7	0.28
Gender (% M)	35	38	0.77
Height (cm)	168.7 ± 4.3	172.2 ± 4.8	0.34
BMI (kg/m^2)	26.7 ± 3.2	27.1 ± 3.2	0.42
Smoking (%)	13	12	0.88
LVMI (g/m^2)	98.3 ± 14.6	96.1 ± 13.2	0.67
Aortic diameter (mm)	29.3 ± 1.5	29.7 ± 1.7	0.42
Transmitral flow E/A	0.89 ± 0.22	0.93 ± 0.23	0.16
Total cholesterol (mg/dL)	211.8 ± 48.7	205.3 ± 45.2	0.27
LDL cholesterol (mg/dL)	130.7 ± 31.3	126.8 ± 27.4	0.33
HDL cholesterol (mg/dL)	55.7 ± 10.0	55.2 ± 13.5	0.40
TG (mg/dL, median-interquartile range)	116.0 (86.0-277.2)	133.7 (93.9-284.3)	0.61
CRP (mg/dl)	0.68 ± 0.20	0.66 ± 0.21	0.72
PWVc-f (m/sec)	11.8 ± 2.6	10.3 ± 1.8	0.04
PINP (ng/mL)	31.3 ± 7.1	24.6 ± 6.2	0.02
CITP (ng/mL)	0.28 ± 0.08	0.32 ± 0.11	0.18
PINP/CITP	118.4 ± 16.6	87.7 ± 13.2	0.04
proMMP-1 (ng/mL)	5.3 ± 1.1	4.7 ± 1.0	0.07
TIMP-1 (ng/mL)	18.9 ± 4.1	22.7 ± 4.3	0.11
proMMP-1 / TIMP-1 ratio	0.8 ± 0.19	0.3 ± 0.12	0.04
β-blockers (%)	45.6	47.2	0.27
ACEI (%)	38.2	39.8	0.23
ARBs (%)	42.4	44.9	0.09
CCBs (%)	38.2	36.5	0.38
Diuretics (%)	33.7	33.1	0.50

BMI – body mass index; LVMI – left ventricular mass index; LDL – low-density lipoprotein; HDL – high-density lipoprotein; TG – triglycerides; CRP – C-reactive protein; PWVc-f – pulse-wave velocity (carotid-femoral); PINP – amino-terminal pro-peptides of pro-collagen type I; CITP – serum telopeptides of type I collagen; ProMMP-1 – pro-metalloproteinase-1; TIMP-1 – tissue inhibitor of metalloproteinase 1; ACEI – angiotensin-converting enzyme inhibitor; ARBs – angiotensin II receptor blockers; CCBs – calcium channel blockers.

Table 2. Basic hemodynamic parameters at rest and peak exercise.

Parameter	Chest pain	No chest pain	p
SBP at rest (mmHg)	135.5 ± 13.0	132.0 ± 14.5	0.31
DBP at rest (mmHg)	80.0 ± 9.0	85.0 ± 9.0	0.75
Mean AP at rest (mmHg)	98.6 ± 13.3	98.8 ± 13.5	0.82
SBP (peak exercise) (mmHg)	185.5 ± 14.0	180.5 ± 11.5	0.38
DBP (peak exercise) (mmHg)	90.0 ± 9.5	95.5 ± 10.0	0.04
Heart rate at rest (b/min)	67 ± 12	72 ± 14	0.44
Heart rate (peak exercise) (b/min)	149.6 ± 16.8	152.2 ± 17.0	0.60
Total exercise time (min:s)	6:16 ± 2:07	6:54 ± 2:16	0.22
METS	8.3 ± 2.3	8.8 ± 2.5	0.27

SBP – systolic arterial pressure; DBP – diastolic arterial pressure; AP – arterial pressure; METS – metabolic equivalents of the task.

pressure were similar at rest and at peak exercise in both groups.

Chest pain, PWVc-f, and indices of collagen turnover

PWVc-f was greater in patients with chest pain compared to those without (Figure 1). Mean PINP levels were also greater in those with chest pain, while CITP levels did not differ significantly between the two groups. The PINP/CITP ratio was significantly higher in patients with chest pain compared to those without (Figure 2). Serum TIMP-1 and proMMP-1 concentrations were similar in the two groups, while the proMMP-1/TIMP-1 ratio was significantly greater in the chest pain group (Figure 2, Table 1).

In a multiple regression analysis model that included age, gender, peak systolic arterial pressure, left ventricular mass index, PINP, and smoking, PINP (t=5.20, p=0.02), peak diastolic blood pressure (t=4.72, p=0.03) and PWVc-f (t=4.60, p=0.03) were associated with the presence of exercise-induced chest pain (Table 3).

After adding the use of antihypertensive drugs to the model via forced entry, PWVc-f (t=2.53, p=0.02) and serum PINP levels (t=2.42, p=0.02) remained significantly associated with the presence of chest pain. No association was found between chest pain and drugs interfering with the renin–angiotensin system (angiotensin converting enzyme inhibitors, t=-1.28, p=0.20; angiotensin receptor blockers, t=-0.93, p=0.35).

Associations between markers of collagen turnover and PWVc-f

Using quartiles of PWVc-f, significant associations were found between PWVc-f and PINP (ANOVA, p=0.02); and between PWVc-f and the proMMP-1/TIMP-1 ratio (ANOVA, p=0.03). In multiple regression analysis where age, gender, systolic arterial pressure, smoking and lipid profile were included, PINP concentrations were also significantly associated with PWVc-f (t=2.34, p=0.02).

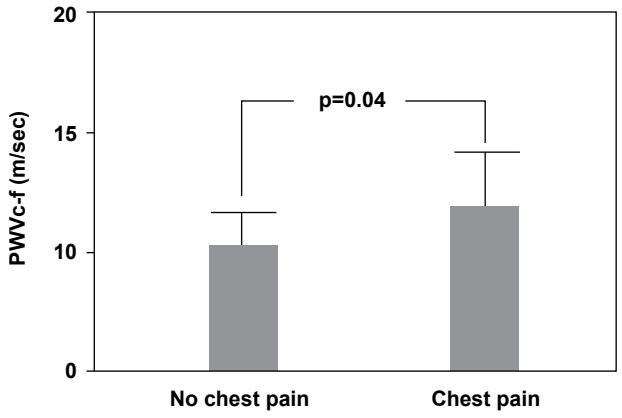

Figure 1. Carotid-femoral pulse wave velocity (PWVc-f) was significantly greater in patients with chest pain compared to those without.

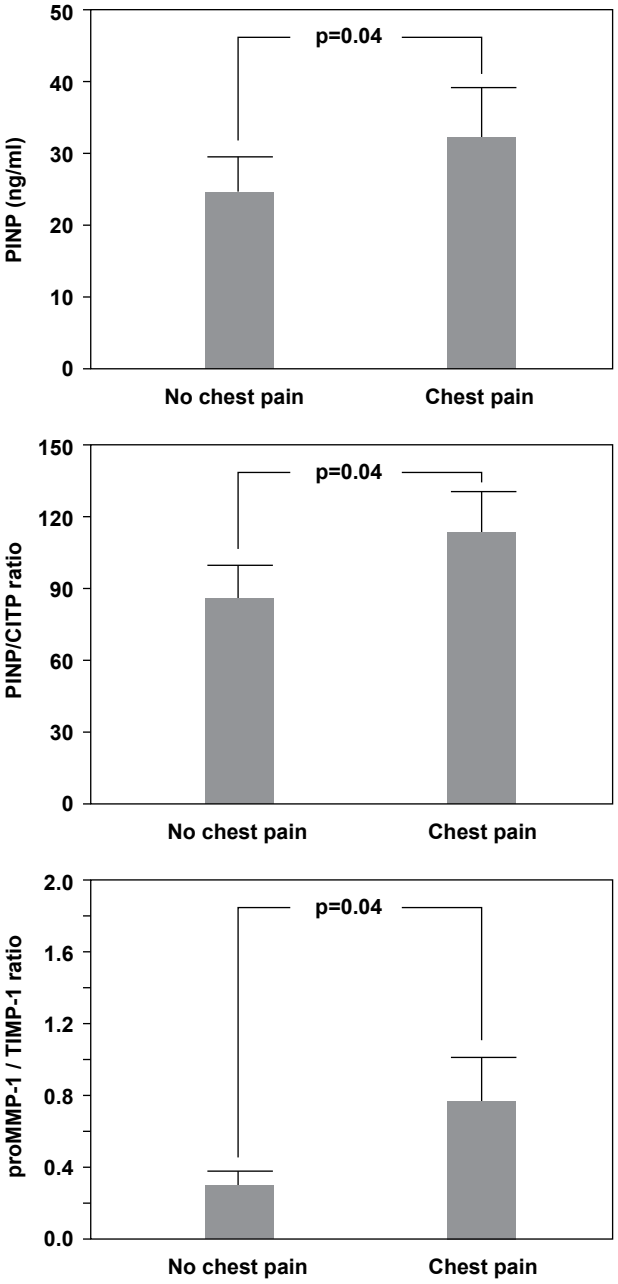

Figure 2. Serum PINP levels, PINP/CITP ratio and proMMP-1/TIMT-1 ratio were significantly higher in patients with chest pain compared to those without. PINP – amino-terminal pro-peptides of pro-collagen type I; CITP – serum telopeptides of type I collagen; ProMMP-1 – pro-metalloproteinase-1; TIMP-1 – tissue inhibitor of metalloproteinase 1.

Table 3. Multiple linear regression analysis for the presence of chest pain (ordinal, R^2=0.46, p=0.0006).

Parameter	Estimate	Std Error	ChiSquare	Prob>ChiSq
PINP	-0.25	0.11	5.20	0.02*
DBP (peak exercise)	0.10	0.04	4.72	0.03*
SBP (peak exercise)	0.18	0.07	1.08	0.34
PWVc-f	-0.74	0.34	4.60	0.03*
PINP/CITP	0.01	0.01	1.30	0.25
Gender	1.25	1.18	1.13	0.29
Age	-0.09	0.09	1.07	0.30
pro-MMP1	0.23	0.23	1.01	0.31
LVMI	0.02	0.02	0.65	0.41
Pro-MMP-1 /TIMP-1	0.33	0.74	0.20	0.65
Smoking	0.21	0.29	0.62	0.17

*Statistically significant.
Abbreviations as in Table 1.

Discussion

Chest pain in patients with angiographically normal coronary arteries is not uncommon.[16,17] Different etiologies have been proposed to explain this phenomenon.[2-7,18] The present study has shown that patients with arterial hypertension and angiographically normal coronary arteries who experience exercise-induced chest pain without evidence of myocardial ischemia on nuclear cardiac imaging had stiffer aortas compared to those without chest pain during exercise. The present study also suggested that alterations in collagen metabolism may affect aortic function in those patients.

A stiff aorta may be related to exercise-induced chest pain in patients with arterial hypertension in many ways (Figure 3). First, a sudden rise in aortic (central) systolic pressure will result in tension of the aortic wall, which may stimulate aortic pain fibers and cause chest pain.[5-8] The aortic adventitia contains pain fibers that run in close relation to those from the heart. Clinical and experimental observations suggest that stretch of the aortic wall may produce chest pain of aortic origin. Balloon inflation – e.g. during angioplasty for aortic coarctation – causes pain that disappears immediately after deflation.[19]

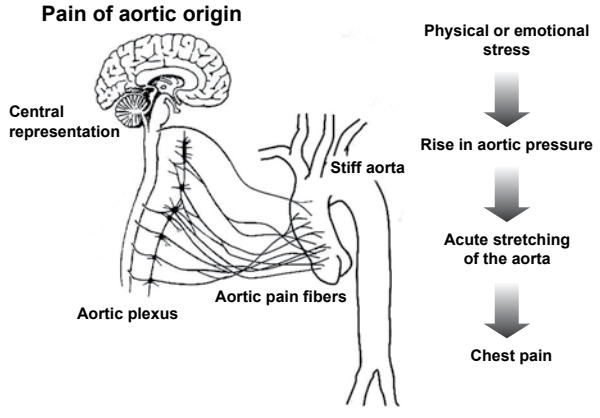

Figure 3. Mechanisms possibly related to chest pain of aortic origin. Schematic presentation.

Second, increased aortic stiffness may be associated with lower diastolic aortic (central) pressure during exercise, thus leading to a decrease in subendocardial blood flow and possibly ischemic chest pain.[20] In this study, the mean diastolic arterial pressure was significantly lower in the chest pain group compared to the no chest pain group. However, central diastolic pressure was not measured during exercise. Additionally, all participants had normal myocardial perfusion imaging studies by protocol. Third, aortic stiffness has been also implicated in impaired cardiac microcirculatory function and reduced coronary flow reserve.[2-4,21] Clinically, these patients may experience myocardial ischemia and chest pain during exercise in the setting of angiographically normal coronary arteries. However, measurements of coronary flow reserve were not performed in the present study. Finally, a combination of multiple factors may be responsible.

Studies have suggested that alterations in collagen turnover may contribute to aortic stiffness in hypertensive patients through a process known as vascular remodeling.[9-11,22-26] The results of the present study confirm and further expand the association between collagen, aortic function and chest pain of aortic origin.

The predominance of the female gender may be

related to the fact that chest pain in patients with angiographically normal coronary arteries is more common in woman.

Collagen turnover is relatively slow and thus it is difficult to determine the contribution of collagen changes to the elastic properties of the arterial wall. Further, a single time point for measuring these markers cannot fully represent the dynamic changes that occur throughout the development of vascular remodeling in the case of arterial hypertension.[27] Circulating markers of collagen turnover may reflect collagen deposition and degradation in any tissue, and serum levels of proMMP-1 and TIMP-1 do not necessarily reflect their activity in the aortic wall. An effort was made to exclude patients with left ventricular hypertrophy, osteoporosis, heart failure, or other conditions that may affect the measurement of collagen turnover indices. Finally, even if it is difficult to decide whether the pain is aortic in origin, the present study demonstrated that hypertensive individuals with chest pain and a normal coronary angiogram had a stiffer aorta compared to those without chest pain.

Clinical implications

In several diseases and conditions that are often associated with a stiff aorta, such as chronic renal failure, coronary artery disease, arterial hypertension, syndrome X, and old age, some episodes of chest pain may be related to the stiff aorta.[28,29] Studies have shown that treatment with renin–angiotensin–aldosterone system antagonists may prevent excessive aortic depositions of collagen in hypertensive animals, and possibly in humans, with a parallel improvement in arterial elastic properties and cardiovascular risk.[30-32]

In conclusion, a stiff aorta may contribute to chest pain during exercise in patients with arterial hypertension and angiographically normal coronary arteries. Alterations in collagen type I turnover that favor excessive collagen deposition in the aortic wall may be responsible for aortic stiffening.[33] The study of the pathophysiological mechanisms of adverse aortic remodeling in patients with arterial hypertension may help us to better understand, identify, monitor and treat these patients with stiff aorta and chest pain of aortic origin.

References

1. Yang EH, Lerman A. Angina pectoris with a normal coronary angiogram. Herz. 2005; 30: 17-25.
2. Brush JE Jr, Cannon RO 3rd, Schenke WH, et al. Angina due to coronary microvascular disease in hypertensive patients without left ventricular hypertrophy. N Engl J Med. 1988; 319: 1302-1307.
3. Opherk D, Mall G, Zebe H, et al. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. Circulation. 1984; 69: 1-7.
4. Hamasaki S, Al Suwaidi J, Higano ST, Miyauchi K, Holmes DR Jr, Lerman A. Attenuated coronary flow reserve and vascular remodeling in patients with hypertension and left ventricular hypertrophy. J Am Coll Cardiol. 2000; 35: 1654-1660.
5. Wooley CF, Sparks EH, Boudoulas H. Aortic Pain: In: Boudoulas H, Stefanadis C eds. The Aorta: Structure, Function, Dysfunction, and Diseases. New York, NY: Informa healthcare USA, Inc.; 2009.
6. Wooley CF, Sparks EH, Boudoulas H. Aortic pain. Prog Cardiovasc Dis. 1998; 40: 563-589.
7. Wooley CF, Sparks EH, Boudoulas H. Aortic pain: the renaissance of cardiovascular pain and the detection of aortopathy. Herz. 1999; 24: 140-153.
8. Vlachopoulos C, Alexopoulos N, Tsiamis E, Stefanadis C. Aortic pain associated with deteriorated aortic elastic properties: an early manifestation of aortopathy. Hellenic J Cardiol. 2006; 47: 176-179.
9. Stakos DA, Tziakas DN, Chalikias GK, Mitrousi K, Tsigalou C, Boudoulas H. Associations between collagen synthesis and degradation and aortic function in arterial hypertension. Am J Hypertens. 2010; 23: 488-494.
10. Olsen MH, Christensen MK, Wachtell K, et al. Markers of collagen synthesis is related to blood pressure and vascular hypertrophy: a LIFE substudy. J Hum Hypertens. 2005; 19: 301-307.
11. Intengan HD, Schiffrin EL. Structure and mechanical properties of resistance arteries in hypertension: role of adhesion molecules and extracellular matrix determinants. Hypertension. 2000; 36: 312-318.
12. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. Am J Cardiol. 1987; 59: 956-960.
13. Vasan RS, Larson MG, Levy D. Determinants of echocardiographic aortic root size. The Framingham Heart Study. Circulation. 1995; 91: 734-740.
14. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation. 1978; 58: 1072-1083.
15. Boudoulas H. Determination of left ventricular mass in clinical practice. J Heart Valve Dis. 1997; 6: 222-227.
16. Boudoulas H, Cobb TC, Leighton RF, Wilt SM. Myocardial lactate production in patients with angina-like chest pain and angiographically normal coronary arteries and left ventricle. Am J Cardiol. 1974; 34: 501-505.
17. Kemp HG Jr, Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. Am J Med. 1973; 54: 735-742.
18. Hasdai D, Holmes DR Jr, Higano ST, Burnett JC Jr, Lerman A. Prevalence of coronary blood flow reserve abnormalities among patients with nonobstructive coronary artery disease and chest pain. Mayo Clin Proc. 1998; 73: 1133-1140.
19. Galal O, Halees Z, Qureshi S, et al. The role of balloon dilation of native aortic coarctation in neonates, infants and chil-

dren. Cardiol Young. 1994;4:126-130
20. Coma-Canella I, Ortuǫo F. Comparison of diastolic blood pressure changes with dobutamine and exercise test. Eur Heart J. 1992; 13: 1245-1250.
21. Nemes A, Forster T, Csanαdy M. Reduction of coronary flow reserve in patients with increased aortic stiffness. Can J Physiol Pharmacol. 2007;85:818-822.
22. Intengan HD, Schiffrin EL. Vascular remodeling in hypertension: roles of apoptosis, inflammation, and fibrosis. Hypertension. 2001; 38: 581-587.
23. Chatzikyriakou SV, Tziakas DN, Chalikias GK, et al. Serum levels of collagen type-I degradation markers are associated with vascular stiffness in chronic heart failure patients. Eur J Heart Fail. 2008; 10: 1181-1185.
24. McNulty M, Mahmud A, Spiers P, Feely J. Collagen type-I degradation is related to arterial stiffness in hypertensive and normotensive subjects. J Hum Hypertens. 2006; 20: 867-873.
25. Ishikawa J, Kario K, Matsui Y, et al. Collagen metabolism in extracellular matrix may be involved in arterial stiffness in older hypertensive patients with left ventricular hypertrophy. Hypertens Res. 2005; 28: 995-1001.
26. Tan J, Hua Q, Xing X, Wen J, Liu R, Yang Z. Impact of the metalloproteinase-9/tissue inhibitor of metalloproteinase-1 system on large arterial stiffness in patients with essential hypertension. Hypertens Res. 2007; 30: 959-963.
27. López B, González A, Díez J. Circulating biomarkers of collagen metabolism in cardiac diseases. Circulation. 2010; 121: 1645-1654.
28. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. Eur Heart J. 1990; 11: 990-996.
29. Stefanadis C, Wooley CF, Bush CA, Kolibash AJ, Boudoulas H. Aortic distensibility abnormalities in coronary artery disease. Am J Cardiol. 1987; 59: 1300-1304.
30. Benetos A, Lacolley P, Safar ME. Prevention of aortic fibrosis by spironolactone in spontaneously hypertensive rats. Arterioscler Thromb Vasc Biol. 1997; 17: 1152-1156.
31. Mahmud A, Feely J. Effect of angiotensin ii receptor blockade on arterial stiffness: beyond blood pressure reduction. Am J Hypertens. 2002; 15: 1092-1095.
32. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010; 55: 1318-1327.
33. Lampropoulos KM, Sokolis DP, Dimitriou CA, et al. The effect of propranolol on aortic structure and function in normotensive rats. Hellenic J Cardiol. 2012; 53: 101-107.