Relationship Between Arterial Stiffness and Myocardial Damage in Patients With Newly Diagnosed Essential Hypertension

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BACKGROUND

Arterial stiffness increases in hypertensive individuals. Arterial stiffness is associated with impairment of systolic and diastolic myocardial function in hypertension (HT). However, the relationship between arterial stiffness and serum heart-type fatty acid–binding protein (H-FABP) levels, a sensitive marker of myocardial damage, has not been previously examined in patients with HT. We investigate the relationship between serum H-FABP levels and arterial stiffness in patients with newly diagnosed HT.

METHODS

We studied 46 (48.5 ± 10.6, years) never-treated patients with HT and age-matched control group of 40 (47 ± 8.6, years) normotensive individuals. H-FABP levels were determined in all subjects. We evaluated arterial stiffness and wave reflections of study population, using applanation tonometry (Sphygmocor). Carotid–femoral pulse wave velocity (PWV) was measured as indices of elastic-type, aortic stiffness. The heart rate–corrected augmentation index (AIx@75) was estimated as a marker of wave reflections.

RESULTS

Carotid–femoral PWV (10.5 ± 2.2 vs. 8.7 ± 1.6, m/s, $P = 0.0001$) and AIx@75 (22.7 ± 9.5 vs. 15 ± 11, %, $P = 0.001$) were significantly higher in patients with HT than control group. H-FABP levels were increased in hypertensive patients compared with control group (21.1 ± 14.8 vs. 12.9 ± 8.5, ng/ml, $P = 0.002$). In multiple linear regression analysis, we found that the body mass index ($\beta = 0.42$, $P = 0.0001$) and carotid–femoral PWV ($\beta = 0.23$, $P = 0.03$) were significant determinants of H-FABP levels.

CONCLUSION

Arterial stiffness is associated with serum H-FABP levels, a sensitive marker of myocardial damage, in patients with newly diagnosed HT.

Am J Hypertens 2008; **21**:989-993 © 2008 American Journal of Hypertension, Ltd.

Arterial stiffness and wave reflections are increasingly used in the clinical assessment of patients with hypertension (HT).[1] Increased arterial stiffness is a determinant of cardiovascular mortality, and larger wave reflections also contribute to cardiovascular risk.[2,3] Carotid–femoral pulse wave velocity (PWV) is an indice of elastic-type, aortic stiffness and the aortic augmentation index (AIx) is a marker of wave reflection derived from aortic pressure wave analysis.[1] Carotid–femoral PWV and AIx are the main methods for assessing arterial stiffness.[1]

Arterial stiffness is an important mechanical property, because of the interaction between left ventricular (LV) ejection and systemic arterial impedance. Arterial stiffness is associated with early and asymptomatic impairment of systolic as well as diastolic myocardial function.[4] Clinical studies have also linked increased aortic stiffness to overt diastolic heart failure.[5] In addition, aortic stiffness influences LV wall thickness and coronary flow reserve.[6,7]

Molecular and scintigraphic studies have demonstrated that myocyte damage occurs in early phases of hypertensive heart disease.[8,9] Heart-type fatty acid–binding protein (H-FABP) is a low–molecular weight (15-kD) cytoplasmic protein, whose role is intracellular transportation of free fatty acid in the cardiomyocytes.[10] H-FABP is abundantly present in the myocardium and is rapidly released into the circulation from the damaged myocardium. We investigate the relationship between serum H-FABP levels, a sensitive marker of myocardial damage, and arterial stiffness in patients with newly diagnosed HT.

METHODS

Study population. In this study, 46 consecutive newly diagnosed hypertensive individuals (48.5 ± 10, years) were enrolled. Forty- age and sex-matched normal subjects (47 ± 8.6, years) were also studied. The diagnosis of HT was established according to the Joint National Committee seventh report.[11] Two-dimensional echocardiographic examinations were performed on each subject. The LV end-systolic diameter and LV

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Received 17 February 2008; first decision 7 April 2008; accepted 6 May 2008; advance online publication 10 July 2008. doi:10.1038/ajh.2008.235

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end-diastolic diameter were measured using the American Echocardiography Society M-mode technique.[12] LV mass was calculated from M-mode records taken on parasternal long-axis images according to the corrected American Society of Echocardiography cube method.[12,13] The subjects with HT included in this study had not taken any antihypertensive therapy previously. Patients with hemolytic, hepatic and renal diseases, diabetes mellitus, heart failure, valvular heart disease, ejection fraction <50%, history of coronary artery disease or acute coronary syndromes, pregnancy, and hypertrophic cardiomyopathy were excluded from the study. Written informed consent was obtained from each subject, and the institutional ethics committee approved the study protocol.

Measurement of H-FABP. Blood samples were drawn from an antecubital vein. The serum was obtained after centrifugation of the blood sample at 3,000 rpm at +4 °C for 10 min, and the serum obtained was stored at −70 °C until analysis. H-FABP levels were measured in subjects using commercially available enzyme-linked immunosorbent assay kits (BioCheck, Foster City, CA). Normal range of H-FABP levels was 1.6–19 ng/ml.[14] Kleine *et al.* indicated an upper normal level of H-FABP as 19 ng/ml.[14] The minimal detectable concentration for the H-FABP assay was 0.25 ng/ml. The inter-assay and intra-assay variations for determining H-HABP were 10 and 8%, respectively.

Blood pressure measurement. Brachial artery blood pressure was measured three times for each patient, using a standard mercury sphygmomanometer, on the right arm and in sitting position after 15 min of rest. Korotkoff phases I and V sounds were used to determine systolic and diastolic blood pressure measurements. Appropriate cuff sizes were chosen for each subject's arm circumference. The average of three measurements was used for the analyses. According to guidelines from the Joint National Committee seventh report, HT was defined as a systolic BP of ≥140 mm Hg or diastolic BP of ≥90 mm Hg.[11]

Measurement of PWV. Carotid–femoral PWV was determined with the foot-to-foot method using the SphygmoCor system (AtCor Medical, Sydney, Australia).[1] Consecutive registrations of the carotid and femoral artery pulse waves are electrocardiogram gated, and thus the time shift between the appearance of wave at the first and the second sites can be calculated. The distance between the two sites was measured on the body surface to determine carotid–femoral PWV in meters/second (m/s). We used the total distance between the carotid and femoral sites of measurement. The average of measurements over a period of 8 s (9–10 cardiac cycles) was calculated after the exclusion of extreme values.

Pressure waveform analysis. Assessment of arterial wall properties and wave reflection characteristics was performed noninvasively using the SphygmoCor system. Radial artery pressure waveforms were recorded at the wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, TX). After 20 sequential waveforms had been acquired and averaged, a validated generalized mathematical transfer function was used to synthesize the corresponding central aortic pressure waveform.[15] AIx and augmentation pressure were derived from this using pressure waveform analysis.[1] The merging point of the incident and the reflected wave (the inflection point) was identified on the generated aortic pressure waveform. augmentation pressure was the maximum systolic pressure minus pressure at the inflection point. The AIx was defined as the augmentation pressure divided by pulse pressure and expressed as a percentage. Larger values of AIx indicate increased wave reflection from the periphery or earlier return of the reflected wave as a result of increased PWV (attributable to increased arterial stiffness). AIx is dependent upon the elastic properties of the entire arterial tree (elastic and muscular arteries). In addition, because AIx is influenced by heart rate, an index normalized for heart rate of 75 bpm (AIx@75) was used in accordance with Wilkinson *et al.*[16] Also systolic tension-time index was obtained as the area under the systolic portion of the aortic pressure wave. Tension-time index has been shown to be related to the working of the heart.[17]

Only high-quality recordings, defined as an in-device quality index of >80% (derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform) and acceptable curves on visual inspection, were included in the analysis. All measurements were performed by the same person (O.G.) with the patient in the supine position in a quiet temperature-controlled room after a brief rest period of at least 5 min.

Statistical analyses. Continuous data are expressed as mean ± s.d. Comparison between two groups was performed using the unpaired *t*-test or nonparametric means test (Mann–Whiteney *U*-test) for continuous variables, and using the Fisher exact test for categoric variables. Pearson's correlation analysis was performed to estimate the correlation between H-FABP levels and other variables. Multiple linear regression analysis was used to identify significant determinants of H-FABP levels. For multiple regression, factors showing a value $P < 0.1$ in univariate analysis were selected. A P value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (Version 10.0; SPSS, Chicago, IL).

RESULTS

Patients characteristics

Baseline clinical and demographic characteristics of the study population are shown in **Table 1**. There were no significant differences in age, gender, smoking, heart rate, body mass index, fasting glucose, serum creatinine, and lipid profiles between the groups. H-FABP level was significantly higher in patients with HT than control (21 ± 14.8 vs. 12.9 ± 8.5, ng/ml, $P = 0.002$) (**Table 1**). As expected, systolic and diastolic blood pressure were higher in patients with HT than in normotensive participants. There were no significant differences in LV diameters and ejection fraction between the groups (**Table 1**). Patients with HT had a greater LV mass index than control (**Table 1**).

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Table 1 | Clinical, echocardiographic and biochemical characteristics of the study groups

	Control ($n = 40$)	Hypertension ($n = 46$)	P
Age (years)	47 ± 8.6	48.5 ± 10.6	0.45
Male (%)	72	54	0.07
BMI (kg/m^2)	29.1 ± 4.1	29.9 ± 4.7	0.43
Smoking (%)	25	28	0.46
Systolic BP (mm Hg)	119 ± 10	160 ± 16	0.0001
Diastolic BP (mm Hg)	77 ± 8	94 ± 10	0.0001
Heart rate (bpm)	68 ± 9	71 ± 12	0.18
LVEDD (mm)	46.5 ± 3.2	47.6 ± 4.1	0.17
LVESD (mm)	29 ± 4	30 ± 3.8	0.37
Ejection fraction (%)	64.8 ± 2.1	65.4 ± 1.8	0.2
LV mass index	94.3 ± 15	118 ± 27	0.0001
Total cholesterol (mg/dl)	197 ± 37	211 ± 38	0.08
Triglyceride (mg/dl)	176 ± 92	188 ± 147	0.67
LDL cholesterol (mg/dl)	128 ± 31	147 ± 78	0.13
HDL cholesterol (mg/dl)	47 ± 15	54 ± 17	0.08
Glucose (mg/dl)	95.3 ± 28	93.4 ± 15	0.7
Creatinine (mg/dl)	0.87 ± 0.1	0.85 ± 0.2	0.67
H-FABP (ng/ml)	12.9 ± 8.5	21.1 ± 14.8	0.002

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; H-FABP, heart-type fatty acid–binding protein; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

Table 2 | Pulse wave analysis and velocity in the study groups

	Normotensive ($n = 40$)	Hypertension ($n = 46$)	P
Central aortic pressure			
Systolic (mm Hg)	108 ± 11	141 ± 17	0.0001
Diastolic (mm Hg)	78 ± 8	93 ± 10	0.0001
Pulse pressure (mm Hg)	30 ± 6	48 ± 14	0.0001
AP (mm Hg)	6 ± 4.3	12.5 ± 7.8	0.0001
AIx	18 ± 11	24 ± 11	0.01
AIx@75 (%)	15 ± 11	22.7 ± 9.5	0.001
CF-PWV (m/s)	8.7 ± 1.6	10.5 ± 2.2	0.0001
TTI	2,193 ± 333	2,818 ± 476	0.0001

AIx@75, heart rate–corrected augmentation index; AP, augmentation pressure; CF-PWV, carotid–femoral pulse wave velocity; TTI, systolic tension-time index.

Table 3 | Bivariate correlation and multiple linear regression analysis between H-FABP and other variables

	Bivariate analysis		Multiple linear regression analysis	
Variables	r	P	β	P
Creatinine	–0.23	0.03	–0.17	0.07
T Cholesterol	0.28	0.008	0.19	0.05
BMI	0.44	0.0001	0.42	0.0001
Peripheral SBP	0.18	0.09	–0.007	0.9
Aortic SBP	0.21	0.05	0.09	0.6
AIx	0.22	0.04	0.1	0.7
AIx@75	0.26	0.01	0.12	0.28
CF-PWV	0.21	0.05	0.23	0.03
TTI	0.19	0.06	–0.12	0.4

AIx@75, heart rate–corrected augmentation index; BMI, body mass index; CF-PWV, carotid–femoral pulse wave velocity; SBP, systolic blood pressure; T, total; TTI, systolic tension-time index.

Pulse wave analysis and velocity

The indices of arterial stiffness and wave reflections of the study population are presented in Table 2. Central aortic systolic, diastolic, and pulse pressure were significantly higher in patients with HT than control subjects (Table 2). Augmentation pressure, AIx, AIx@75, carotid–femoral PWV, and tension-time index were significantly higher in patients with HT than control subjects (Table 2).

Determinants of H-FABP

In bivariate correlation analysis, significant correlation was found between H-FABP levels and creatinine, total cholesterol, body mass index, brachial systolic pressure, aortic systolic pressure, AIx@75, and carotid–femoral PWV (Table 3). No significant relationships were observed between H-FABP and age ($r = 0.07$, $P = 0.48$), LV end-diastolic diameter ($r = 0.02$, $P = 0.8$) LV end-systolic diameter ($r = 0.09$, $P = 0.4$), ejection fraction ($r = –0.1$, $P = 0.3$), and LV mass index ($r = 0.12$, $P = 0.6$). H-FABP levels were significantly higher in female (24 ± 15 vs. 13 ± 9, $P = 0.001$). Multiple regression analyses were performed for identifying factors that determine the levels of H-FABP. Significant determinants of H-FABP levels were body mass index ($\beta = 0.42$, $P = 0.0001$) and carotid–femoral PWV ($\beta = 0.23$, $P = 0.03$) (Table 3). Besides, an increased tendency toward a relationship was demonstrated between the H-FABP levels and total cholesterol ($\beta = 0.19$, $P = 0.05$) and creatinine ($\beta = –0.17$, $P = 0.07$) in the multiple regression analyses. Gender was not associated with H-FABP levels ($\beta = –0.008$, $P = 0.9$) in multiple regression analyses.

DISCUSSION

In this study, we investigated the relationship between arterial stiffness and myocardial damage in patients with newly diagnosed HT. We have found that H-FABP, a marker of myocardial damage, was significantly increased in patients with HT compared with normotensive subjects. Also we found that carotid–femoral PWV was an independent determinant of H-FABP levels.

We found that H-FABP levels were approximately twofold higher in HT patients compared with controls. Previous studies have demonstrated that myocyte damage occurs in early phases of hypertensive heart disease.[8,9] Mechanical and humoral factors that are stimulated in patients with HT may induce the myocyte damage. The presence of ultrastructural alterations in

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hypertensive heart is confirmed by some morphological characteristics in autopsy studies, such as the increase of collagenic volume fraction, necrotic myocytes, and fibrosis.[18] Anversa *et al.* showed that contractile disturbances of cardiomyocytes and changes of the extracellular matrix leading to myocardial fibrosis, apoptotic cardiomyocyte loss is now considered one of the determinants of the structural remodeling implicated in the transition from LV hypertrophy to heart failure in arterial HT.[19] Rossi demonstrated that fibrosis and connective tissue matrix replace areas of myocyte loss in history of systemic HT without valvular deformities and no evidence of ischemic disease at the postmortem examination.[20] Recent evidence demonstrates that cardiomyocyte apoptosis is abnormally stimulated in the heart of animals and humans with arterial HT.[21,22] Furthermore, Gonzales *et al.* demonstrated that apoptosis is abnormally stimulated in patients with essential HT and no evidence of cardiomyopathy or heart failure is seen.[23] Mitochondrial production of adenosine triphosphate is diminished in the hypertensive myocardium.[24] If adenosine triphosphate levels fall profoundly, the mode of cell death would switch to necrosis.[8] In addition, Setsuta *et al.* showed that ongoing myocardial damage detected by H-FABP is related to cardiomyocyte apoptosis in patients with heart failure.[25] It has been suggested that intracellular calcium level is increased in hypertensive patients.[26] Nakayama *et al.* show that myocyte necrosis can be precipitated through calcium overload.[27]

Early alterations of myocardial function was demonstrated by new imaging techniques. Unlu *et al.* have showed myocyte damage in antimyosin scintigraphy of hypertensive patients with normal ejection fraction.[9] Thallium perfusion defects may be observed in hypertensive patients without coronary artery disease.[28] In a study conducted by Stoylen *et al.*, hypertensive patients with normal LV global systolic function demonstrated strain rate reduction in comparison with healthy controls.[29] Videodensitometric analyses of myocardial ultrasound texture is able to detect early myocardial damage in hypertensive LV hypertrophy.[30] These different methodological studies suggest that myocardial damage may occur in early phases of hypertensive heart disease. H-FABP is cytosolic protein in cardiomyocytes and is released rapidly into circulation in small amounts after myocardial damage.[10] As mentioned, pathophsiologic change of cardiomyocytes may induce H-FABP release in patients with HT.

Compared with normotensive individuals, carotid–femoral PWV and AIx@75 were higher in our hypertensive subjects, indicating a deterioration in arterial stiffness and wave reflections. AIx@75, a marker of wave reflections, was not associated with H-FABP levels. Carotid–femoral PWV, as indices of elastic-type, aortic stiffness, is an important determinant of H-FABP levels. Carotid–femoral PWV, a classical measure of arterial stiffness, is widely used to assess the elastic properties of the arterial tree and is a strong predictor of cardiovascular complications in different clinical settings, including essential HT.[1,31–33] Body mass index was also significantly associated with H-FABP levels in our study. Niizeki *et al.* showed that H-FABP levels were independently affected by body mass index in general population.[34] In the present study, there was a trend for a relationship between the H-FABP levels and total cholesterol and creatinine. However, this association was not statistically significant. In a previous study, creatinine clearance was significantly associated with H-FABP levels.[34] Systemic factors may contribute to the high H-FABP levels.

H-FABP is useful for detecting myocardial injury and predicting recurrent cardiac events in acute coronary syndromes and in congestive heart failure patients.[35] H-FABP is more sensitive to detect ongoing myocardial damage than troponin T in patients with heart heart failure.[36] Also H-FABP is more sensitive than troponin, creatine kinase isoenzyme MB, and myoglobin in acute coronary syndromes when measured in the early hours after symptom onset.[37,38]

Previous studies have shown that arterial stiffness increases in hypertensive individuals.[39] Fernandes *et al.* show that arterial stiffness is associated with early and asymptomatic impairment of systolic as well as diastolic myocardial function.[4] Schillaci *et al.* found that with increasing age, aortic PWV becomes related to LV concentric remodeling and to depressed LV systolic function.[40] Aortic stiffness also influences LV wall thickness and coronary flow reserve.[6,7] Taking into account the mechanisms mentioned above, increased stiffness of aorta may contribute to the development of myocardial damage in patients with HT.

Limitations of study

Firstly, small number of patients is a potential limitation of this study. Large prospective studies are needed to establish the relationship between arterial stiffness and myocardial damage in hypertensive subjects. In addition, lack of assessment of myocardial damage by new imaging techniques (nuclear magnetic resonance and radionuclide imaging) is a limitation of our study. However, demonstrating myocardial damage using H-FABP is more easy and practical than new imaging methods. It has been suggest that H-FABP was released in different cell types.[41] Other potential sources of H-FABP may affect the interpretation of the data.

In conclusion, we found a significant relationship between carotid–femoral PWV and increased serum H-FABP levels in patients with newly diagnosed HT. Arterial stiffness may have an impact on development of myocardial damage in hypertensive patients.

Acknowledgment: This study was supported by the Karadeniz Technical University Fund.

Disclosure: The authors declared no conflict of interest.

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