THE CORRELATION OF CAROTID ARTERY STIFFNESS WITH HEART FUNCTION IN HYPERTENSIVE PATIENTS

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BACKGROUND: The strength of each heart beat and the stiffness of large arteries contribute to blood pressure (BP). When the large arteries are stiff and their resistance greater, the afterload increases and this may change the function of the heart. However, the relation between common carotid artery stiffness and heart function in hypertensive patients has not been clarified.

METHODS: Two hundred and twenty hypertensive patients underwent transthoracic and carotid echocardiography. Measurements of local arterial stiffness were taken at the right common carotid artery level and stiffness parameter ($\beta$), pressure-strain elasticity modulus and intima-media thickness were calculated. Brachial cuff BP was measured just before starting the carotid study. The patients with any cardiovascular disease, diabetes mellitus, stroke, transient ischemic attack, or carotid stenosis were excluded.

RESULTS: Carotid artery stiffness parameter ($\beta$) was correlated with age and left ventricular mass index ($p < 0.005$). Even though $\beta$ was not correlated with LV systolic function, it was inversely correlated with diastolic function as measured by early mitral annular velocity ($p < 0.001$) and the index of left atrial (LA) pressure (early diastolic mitral inflow E velocity/e') increased ($p = 0.001$). In logistic regression, diastolic dysfunction was affected by age (beta -0.385, $p = 0.001$), LA volume index (beta 0.175, $p = 0.013$) and $\beta$ (beta -0.273, $p = 0.019$).

CONCLUSION: In hypertensive patients, changes in carotid artery stiffness can affect the diastolic function, independent of age and LA volume index. Therefore, measurements and control of carotid stiffness can play an important role in the prevention of diastolic heart failure.

KEY WORDS: Carotid stiffness · Diastolic function · Female.
METHODS

STUDY SUBJECTS
We reviewed approximately 300 hypertensive patients who had transthoracic and carotid echocardiography on the same day. Hypertension was defined based on SBP ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg calculated as the means of 2 blood pressure measurements, patient's self-report of previous diagnosis of hypertension, or the undertaking of medical treatment thereof. The patients with diabetes, dyslipidemia, history of cardiovascular disease (coronary artery disease, congestive heart failure, stroke, transient ischemic attack or intermittent claudication) and carotid artery stenosis were excluded.

For the calculation of the carotid stiffness parameters, the blood pressure (BP) taken before the carotid examination was entered into the program. The BP measurements taken before echocardiography were used for the calculation of PP (systolic BP - diastolic BP). Weight (in kilograms) and height (in meters) were measured using standard techniques, and body mass index (BMI) was calculated as body weight divided by height squared. Body surface area was calculated using the DuBois formula \(0.20247 \times \text{height}^{0.725} \times \text{weight}^{0.425}\). This study was approved by the institutional ethics board, and an informed consent was obtained from all participants.

TWO-DIMENSIONAL AND DOPPLER ECHOCARDIOGRAPHY
Echocardiography was performed with an ultrasound system (Vivid 7 GE Vingmed, Horten, Norway) with a 2–4-MHz transducer. Standard 2-dimensional measurements [end-diastolic and end-systolic dimensions, ventricular septum and posterior wall thickness, left atrial volume index (LAVI), left ventricular mass index (LVMI), left ventricular (LV) outflow tract diameter] including LV ejection fraction were taken with the patient in the left lateral position.

Through the apical 4 chamber window, a 1- to 2-mm pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities was recorded for the duration of 5 to 10 cardiac cycles. The following parameters were obtained: peak velocity of early filling (E) and late (A) filling, deceleration time of the E wave velocity, and ratio of E over A.

Pulse Doppler tissue imaging was carried out in the four-chamber view at the septal mitral annular level. The peak velocity of myocardial systolic wave (S'), early peak (e') and atrial (A') diastolic wave (in centimeters per second), and the E/e' ratio were recorded.

CAROTID STIFFNESS
High resolution B-mode ultrasound imaging of the carotid arteries was performed using a GE scanner (with a 12-MHz transducer; Vivid 7 GE Vingmed, Horten, Norway) with patient in the supine position. Every effort was made to examine the participants in the morning after an overnight fasting and smoking cessation. The best acoustic window was identified with the jugular vein above the common carotid artery and a series of images were acquired over a 20 second period. Five to six cardiac cycles on average were used for the estimation of carotid diameters. BP was determined by upper arm sphygmomanometry during carotid artery measurements. Strain represents a ratio of the amount of stress deformation relative to the unstressed state, and stiffness is a dimensionless quantity that expresses the tendency of an individual’s arteries to deform under a given change in blood pressure. We therefore defined strain as (Ds - Dd) / Dd, stiffness as STIFF (β index) = ln (Ps / Pd) / Strain, and pressure-strain elasticity modulus (Ep) as (pressure - strain elasticity modulus) = (Ps - Pd) / (Ds - Dd) / Dd, where Ps is systolic BP, Pd is diastolic BP, Ds is arterial systolic diameter, and Dd is arterial diastolic diameter.

The interobserver and intraobserver variabilities for measuring have been compared in 40 consecutive measurements, and were 4.2 and 3.4%, respectively.

STATISTICAL ANALYSIS
We performed Pearson’s correlation analysis to assess the univariate correlations between arterial stiffness parameters, intima-media thickness (IMT), and LV structure and functional variables. Pearson’s correlation analysis was also used to evaluate whether age, PP, sex, and BMI were associated with arterial stiffness, systolic and diastolic function, and LV structure. Covariate analysis was then applied to make an adjustment for the effect of age as well as for the combined effects of age, PP, sex, and BMI. The defining level of statistical significance (p value) was set at 0.05. Data analysis was performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

RESULTS
The main characteristics of the study population are reported in Table 1.

| Table 1. The main characteristics of the study population |
|---------------------------------|----------------|
| Age (yr)                        | 54.5 ± 12.1    |
| Sex (M : F)                     | 117 : 104      |
| HTN duration (month)            | 24 ± 10        |
| Height (cm)                     | 141.4 ± 22.4   |
| Weight (kg)                     | 76.0 ± 13.7    |
| BMI (kg/m²)                     | 24.8 ± 3.5     |
| LVMI (m²)                       | 1.71 ± 0.20    |
| SBP (mmHg)                      | 130.2 ± 18.4   |
| DBP (mmHg)                      | 79.1 ± 11.1    |
| PP (mmHg)                       | 51.12 ± 13.53  |
| HR (bpm)                        | 71.1 ± 10.7    |

The data are given as mean ± SD. HTN: hypertension, BMI: body mass index, BSA: body surface area, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, HR: heart rate.
The mean age of the participants was 54.5 ± 12.1 years. Fifty three percent of the patients were males. All patients satisfied the hypertension criteria. Their BP was relatively well controlled, therefore the mean value of LV dimension, LVMI, LV ejection fraction and LAVI were not so deviated within normal range.

The echocardiographic parameters and arterial stiffness variables are shown in Table 2.

Correlations between beta index and diastolic function indices are presented in Table 3. Beta index, that is carotid stiffness, was found to have negative correlations with female sex and e’ (early diastolic tissue velocity), while there was a positive correlation between beta index and age, LAVI, LVMI, the late portion of diastolic function (A wave) and E over e’ (E/e’).

Age, SBP, LVMI, A wave and E over e’ (E/e’) were also positively correlated with Ep and that was negatively correlated with e’ wave. As expected, age was correlated significantly with arterial stiffness and diastolic functional variables. IMT was negatively correlated with age, but not with LV diastolic parameters. In logistic regression, diastolic dysfunction was affected by age (beta -0.385, p = 0.001), female sex (beta -0.270, p = 0.035), LAVI (beta 0.175, p = 0.013) and β (beta -0.273, p = 0.019) (Table 4).

Therefore, we found that carotid stiffness was independently associated with LV diastolic dysfunction even after controlling for age, sex, LAVI and LVMI (Table 4).

**DISCUSSION**

To the best of our knowledge, there are some data available on the association between arterial stiffness and diastolic function among subjects with cardiovascular risk factor, especially metabolic syndrome or obesity, and those with manifested arterial disease. However, little is known about this association in patients only with hypertension without any other diseases.

It has been shown that the local measurement of arterial stiffness may be useful for the detection of early arterial changes. Several plausible pathways exist whereby arterial compli-

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**Table 2. The echocardiographic parameters and arterial stiffness variables**

| Parameter            | Mean       |
|----------------------|------------|
| LVIDD (mm)           | 46.2 ± 4.64 |
| LVISD (mm)           | 31.7 ± 4.01 |
| LVMI (g/m²)          | 91.1 ± 20.52 |
| LAVI (mL/m²)         | 23.7 ± 6.43 |
| Doppler parameters   |            |
| E/A (cm/sec)         | 65.3 ± 14.8/61.0 ± 15.2 |
| DT (sec)             | 212.7 ± 37.7 |
| E (cm/sec)           | 64.2 ± 12.6 |
| e’ (cm/sec)          | 5.93 ± 1.35 |
| A’ (cm/sec)          | 7.85 ± 1.61 |
| S’ (cm/sec)          | 6.91 ± 1.36 |
| E/e’                 | 11.2 ± 2.41 |
| Stiffness index      |            |
| Beta index           | 4.16 ± 2.03 |
| Ep                   | 95.6 ± 508.6 |
| IMT (Rt, mm)         | 0.76 ± 0.15 |

The data are given as mean ± SD. LVIDD: left ventricular internal diastolic dimension, LVISD: left ventricular internal systolic dimension, LVMI: left ventricular mass index, LAVI: left atrial volume index, E: early diastolic mitral inflow velocity, A: late diastolic mitral inflow velocity, DT: deceleration time, e’: early diastolic tissue velocity, A’: late diastolic tissue velocity, Ep: pressure-strain elasticity modulus, IMT: intima media thickness.

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**Table 3. The correlation of carotid stiffness and IMT with heart function**

| Parameter   | Beta index | Ep | IMT |
|-------------|------------|----|-----|
| Age (yr)    | 0.353      | 0.286 | 0.341 |
| Sex (female)| -0.256     | -0.186 | -0.216 |
| SBP (mmHg)  | 0.153      | 0.392 | 0.104 |
| DBP (mmHg)  | -0.119     | 0.123 | -0.007 |
| LVEF (%)    | -0.004     | -0.017 | 0.114 |
| LAVI (mL)   | 0.170      | 0.125 | 0.055 |
| LVMI (g/m²) | 0.164      | 0.146 | 0.113 |
| E (m/sec)   | -0.161     | -0.134 | -0.094 |
| A (m/sec)   | 0.289      | 0.303 | 0.203 |
| e’ (cm/sec) | -0.513     | -0.326 | -0.257 |
| S’ (cm/sec) | -0.119     | -0.078 | -0.190 |
| E/e’        | 0.251      | 0.227 | 0.221 |

The data are given as p value. Beta index, that is carotid stiffness, was found to have negative correlations with female sex and e’ (early diastolic tissue velocity), while there was a positive correlation between beta index and age, LAVI, LVMI, the late portion of diastolic function (A wave) and E over e’ (E/e’). Age, SBP, LVMI, A wave and E over e’ (E/e’) were also positively correlated with Ep and that was negatively correlated with e’ wave. As expected, age was correlated significantly with arterial stiffness and diastolic functional variables. IMT was negatively correlated with age, but not with LV diastolic parameters. In logistic regression, diastolic dysfunction was affected by age (beta -0.385, p = 0.001), female sex (beta -0.270, p = 0.035), LAVI (beta 0.175, p = 0.013) and β (beta -0.273, p = 0.019) (Table 4).

**The echocardiographic parameters and arterial stiffness variables**

| Parameter            | Mean       |
|----------------------|------------|
| 2D parameters        |            |
| LVIDD (mm)           | 46.2 ± 4.64 |
| LVISD (mm)           | 31.7 ± 4.01 |
| LVMI (g/m²)          | 91.1 ± 20.52 |
| LAVI (mL/m²)         | 23.7 ± 6.43 |
| Doppler parameters   |            |
| E/A (cm/sec)         | 65.3 ± 14.8/61.0 ± 15.2 |
| DT (sec)             | 212.7 ± 37.7 |
| E (cm/sec)           | 64.2 ± 12.6 |
| e’ (cm/sec)          | 5.93 ± 1.35 |
| A’ (cm/sec)          | 7.85 ± 1.61 |
| S’ (cm/sec)          | 6.91 ± 1.36 |
| E/e’                 | 11.2 ± 2.41 |
| Stiffness index      |            |
| Beta index           | 4.16 ± 2.03 |
| Ep                   | 95.6 ± 508.6 |
| IMT (Rt, mm)         | 0.76 ± 0.15 |

The data are given as mean ± SD. LVIDD: left ventricular internal diastolic dimension, LVISD: left ventricular internal systolic dimension, LVMI: left ventricular mass index, LAVI: left atrial volume index, E: early diastolic mitral inflow velocity, A: late diastolic mitral inflow velocity, DT: deceleration time, e’: early diastolic tissue velocity, A’: late diastolic tissue velocity, Ep: pressure-strain elasticity modulus, IMT: intima media thickness.
ance may contribute to the pathological changes in the LV that form the substrate for diastolic dysfunction. Increased stiffness of conduit arteries is associated with higher velocity of transmission of the pulse wave generated by LV ejection; early return of reflected waves that arrive back at the heart during LV systole may lead to augmentation of the central aortic pressure wave amplitude, thus increasing LV afterload and central PP. Increased afterload may promote myocyte hypertrophy and may also directly slow LV relaxation. The arterial stiffness leads to increased PP and to LV hypertrophy, which is one of the major determinants of cardiac diastolic dysfunction. Furthermore, in patients with presumed diastolic heart failure (HF) clinical HF with preserved ejection fraction, Hundley et al. observed reduced proximal aortic distensibility, which is itself associated with diastolic dysfunction. However, in this study, even in subjects with hypertension with normal LV mass, carotid stiffness was increased with diastolic dysfunction. Therefore the measurement of carotid stiffness may be a good tool for early detection of decreased carotid dispensability.

The relationship between elastic properties of the arteries and LV diastolic function has been demonstrated in different clinical scenarios. Sakane et al. found in 119 patients that cardio-ankle vascular index was independently related to E/A ratio in patients with preserved LV ejection fraction. Abhayaratna et al. demonstrated that in a cohort of 188 patients (aged ≥ 65 years), increasing arterial stiffness detected with applation tonometry was associated with the severity of LV diastolic dysfunction. Vinereanu et al. showed that arterial stiffness was inversely related to long axis LV function (systolic and early diastolic mitral annular velocities) and LV flow propagation velocity. In a study on a hypertension patient group, Mottram et al. showed that arterial compliance, measured using application tonometry, is an independent predictor of diastolic dysfunction. These authors also showed that arterial stiffness was independently related to early diastolic tissue velocity (=e') and suggested a possible causal link through the promotion of subendocardial ischaemia.

The relation between arterial compliance and diastolic dysfunction may be particularly important with respect to hypertensive women, who have a higher prevalence of diastolic HF than men. Experimental and clinical studies suggest that, in response to increased afterload, women exhibit a greater degree of concentric remodelling which as discussed is associated with both arterial stiffness and diastolic dysfunction. In addition, several studies have reported increased values of arterial stiffness in women. In the present study, sex was associated with reduced E’ velocity and independently related to arterial stiffness in hypertensive patients (Table 3). After adjustment for other factors, female sex was independently predictive of diastolic dysfunction. In addition, the results indicate that an interaction between sex and arterial compliance may be important, such that arterial dysfunction may contribute to diastolic dysfunction in hypertensive women to a greater extent than in hypertensive men who also have diastolic dysfunction.

In this article, we calculated carotid artery stiffness using distensibility (strain) and pressure-strain elasticity modulus. Since this procedure enables relatively accurate data to be acquired easily and other cardiovascular events to be predicted, it would be important to pay more attention to performing the assessment of arterial stiffness in patients with early-stage hypertension or normal LV mass to prevent LV diastolic dysfunction and maintain normal blood pressure especially in women.

### Table 4. Univariate and multivariate analyses for diastolic dysfunction (e’)

|               | Univariate analysis | Multivariate analysis |
|---------------|---------------------|-----------------------|
| Age (yr)      | -0.610              | -0.385                |
| Sex           | -0.358              | -0.270                |
| SBP (mmHg)    | -0.172              | -0.083                |
| LVMI (g/m²)   | -0.371              | -0.279                |
| LAVI (mL)     | -0.189              | 0.175                 |
| IMT (mm)      | -0.257              | 0.013                 |
| A (m/sec)     | -0.460              | -0.273                |
| Beta index    | -0.354              | 0.019                 |

SBP: systolic blood pressure, LVMI: left ventricular mass index, LAVI: left atrial volume index, IMT: intima-media thickness, A: late diastolic mitral inflow velocity

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