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Alterations of carotid arterial mechanics preceding the wall thickening in patients with hypertension

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ABSTRACT

Background and aims: Carotid intima-media thickness (cIMT) is an established surrogate marker of atherosclerosis. However, cIMT may not reflect the whole arterial changes occurring in various pathologic conditions, such as hypertension. The aim of this study was to evaluate whether vascular properties of carotid artery (CA) in patients with hypertension differ from those of patients with diabetes and controls before the progression of cIMT.

Methods: Vascular properties of CA were assessed in 402 consecutive asymptomatic subjects who have normal cIMT (131 with hypertension, 151 with diabetes mellitus, and 120 controls). Conventional carotid stiffness indices calculated from vessel diameter and blood pressure, and parameters from velocity-vector imaging (VVI), including vessel area, fractional area change (FAC), radial velocity, circumferential strain, and strain rate were measured to assess the differences between the groups.

Results: In univariate analysis, both patients with hypertension and diabetes showed higher elastic modulus, lower distensibility coefficients and FAC of VVI than those of controls. However, when adjusting for baseline covariates, only FAC (odds ratio [OR] = 0.82, 95% confidence interval [CI] = 0.70–0.97, $p = 0.025$) and vessel area (OR = 2.84, 95% CI = 1.64–4.91, $p < 0.001$) discriminated CA of patients with hypertension from those of controls. Also, patients with hypertension showed larger vessel area than diabetes (OR = 2.58, 95% CI = 1.75–3.80, $p < 0.001$) independent of baseline covariates. No significant vascular parameter was found to discriminate patients with diabetes from controls after adjustments.

Conclusion: Despite normal cIMT, the CA of hypertensive patients was stiffer than those of controls and positive remodeling preceded the wall thickening independent of baseline covariates.

1. Introduction

Among the various parameters of vascular properties, carotid intima-media thickness (cIMT) has been suggested as a surrogate measure of vascular alterations, and several studies have shown that increasing cIMT is associated with subsequent coronary heart disease and stroke [1,2]. Since it is non-invasive, reproducible, and simple, measurement of cIMT with ultrasonography is widely used to quantify the extent of subclinical disease in individuals with cardiovascular (CV) risk factors and to follow up in interventional studies. However, cIMT may not reflect the whole arterial changes occurring in various pathologic conditions, such as hypertension. Before the progression of the intima and media thickening, the carotid artery (CA) may experience functional alterations (such as wall stiffening), of which the occurrence is also associated with an increased risk of CV morbidity or mortality by augmenting arterial impedance and resultant increase in the afterload of the heart [3]. Recently, with advancements in ultrasound (US) techniques, a novel automated speckle-tracking method using velocity-vector imaging (VVI) software has facilitated the instantaneous quantification of CA mechanics and we have shown the altered vascular properties associated with aging [4] and arteriopathies [5,6] such as Takayasu's arteritis and Marfan syndrome. In this study, we aimed to assess whether vascular properties of CA before the progression of cIMT in patients with hypertension are abnormal and different from those of patients with diabetes and controls using VVI

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analysis.

2. Methods

2.1. Study population

A total of 1024 subjects were recruited from among patients with hypertension or diabetes and healthy subjects. They underwent carotid US for CV risk stratification and general health screening. Among them, 402 asymptomatic subjects were consecutively identified if they had: 1) normal cIMT free from atheromatous plaque on carotid US; 2) hypertension, were normoglycemic, and had no evidence of secondary hypertension; 3) type 2 diabetes mellitus, were normotensive, and were without evidence of macrovascular or microvascular (microalbuminuria, retinopathy, or neuropathy) complications; and 4) no other evidence of CV, cerebrovascular, renal disease or arrhythmia.

The study population consisted of 131 patients with hypertension (age 31–75 years, 53% females), 151 patients with type 2 diabetes mellitus (age 36–71 years, 44% females), and 120 healthy subjects (age 30–77 years, 47% females) who served as a control group with similar age and gender. Hypertension was defined as those individuals who had a systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, or those who were treated with antihypertensive medications and the diagnosis of diabetes mellitus was based on the criteria of the American Diabetes Association [7]. Dyslipidemia was defined as a total serum cholesterol >220 mg/dL (5.69 mmol/L), serum triglycerides > 150 mg/dL (1.71 mmol/L), and/or the current use of lipid-lowering agents. The protocol of the study was approved by our institutional ethics committee and written informed consent was obtained from all subjects.

2.2. BP measurement

Before the US examination, brachial blood pressure was measured using an oscillometric automatic device (Omron HEM 1000, Omron Healthcare, Kyoto, Japan) by averaging three consecutive measurements in the supine position after at least 5 min rest in a quiet comfortable environment. Phase I and V Korotkoff sounds from the brachial artery were used for the Ps and Pd, respectively. The pulse pressure (PP) was calculated as PP = Ps − Pd, where Ps and Pd are systolic and diastolic blood pressures. Before assessment of carotid US, heart rate (HR) was measured for $\geq$ 30 s after 5 min of rest.

2.3. Carotid ultrasound

Carotid US studies were performed by a single registered vascular technologist (P.S.H) who was blinded to the subject's clinical status with a high-resolution B-mode ultrasound (Acuson Sequoia 512, Siemens Acuson, Mountain View, CA) equipped with an 8-MHz linear-array transducer. Data were stored as digital cineloops for subsequent offline analysis, and a single experienced reader (K.S.A) who was blinded to the subject's clinical status performed all measurements. The subjects were kept in the supine position with their heads turned approximately 45° away from the side examined. A preliminary scan of internal, external, and common carotid arteries (CCA) was done to evaluate the presence of plaques and/or stenoses. Plaque was defined as either cIMT >1.3 mm or the presence of focal thickening at least 50% greater than the neighboring site on initial US examination.

The mean cIMT was calculated as the average of three consecutive manual measurements at the far wall of the carotid artery 1 cm proximal to the carotid bulb of both CCAs from leading edge (lumen-intima) to leading edge (media-adventitia) during end-diastole. Upper limit values of the normal cIMT were defined as less than the 75th percentile for measurements taken in 1229 healthy Korean adults according to age and gender groups [8]. Average end-diastolic (Dd) and peak-systolic (Ds) internal diameters were assessed in three cycles as the distance between the intima-lumen interface at the near wall and the lumen-intima interface at the far wall of both CCAs (1 cm proximal to the beginning of the carotid bulb).

Transverse images of both CCAs (1 cm proximal to the carotid bulb) were stored using acoustic capture for off-line analysis with the VVI workstation (Syngo®, US Workplace, Siemens, Mountain View, CA, USA). VVI fundamentally uses a two-dimensional speckle tracking method, from which the blood-tissue border was traced manually over one frame of a cine loop, and by which the ultrasonic speckles were automatically tracked vessel wall motion dividing into six segments (Fig. 1A). Apart from circumferential vessel area at end-diastole, VVI also provides instantaneous quantitative measures of vessel deformation through the cardiac cycle, including fractional area change (FAC), radial velocity (RV), circumferential strain (S) and strain rate (SR) (Fig. 1B). All of the CA measurements on both sides were averaged to obtain the mean value.

2.4. Carotid artery stiffness indices

Carotid arterial stiffness indices were derived according to the following formula: β, an index of arterial wall stiffness, was determined as ln (Ps/Pd)/[(Ds-Dd)/Dd] [9,10], where Ps and Pd are systolic and diastolic blood pressures, and Ds and Dd are systolic and diastolic internal diameters of the artery, respectively. The cross-sectional compliance coefficient in mm^2/kPa was given as: $\pi \times [2 \times (Ds\text{-}Dd) \times Dd + (Ds\text{-}Dd)^2]/4 \times (PP)$, where PP indicates pulse pressure (Ps − Pd) [11]. The distensibility coefficient in 10^{-3}/kPa was calculated as: $[2 \times (Ds\text{-}Dd) \times Dd + (Ds\text{-}Dd)^2]/PP \times Dd^2$ [11]. Peterson's elastic modulus in $10^2 \times$ kPa was defined as: [PP/(Ds-Dd)] × Dd [12]. Finally, Young's elastic modulus in $10^2 \times$ kPa/mm was defined as [PP/(Ds-Dd)] × (Dd/cIMT) [13].

2.5. Laboratory

For blood biochemistry analyses, serum glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol were measured by standard enzymatic laboratory methods (Vitros 250; Johnson/Johnson, New Zealand) after 10 h of overnight fasting. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula.

2.6. Observer and test-retest reliability

Intraobserver and inter-observer reliability was assessed in a randomly selected 150 patients and test-retest variability was assessed in a randomly selected 30 patients. VVI datasets were analyzed for intraobserver reliability by 1 investigator (K.S.A) on the same patients 4 weeks apart in a random order. The interobserver reliability was assessed by a second investigator (P.S.H), who was blinded to the previous results on the same patients. To assess test–retest reliability, a complete re-study was performed within 1 h after the first study without alteration of hemodynamics or therapy.

2.7. Statistical analysis

Data are expressed as mean ± SD or as frequencies and percentages. We compared means of each continuous variable of the