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Usefulness of controlled attenuation parameter for detecting increased arterial stiffness in general population

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ABSTRACT

Background: Liver fibroscan has recently been suggested as an alternative method to measure liver steatosis noninvasively. In this study, we evaluated usefulness of controlled attenuation parameter (CAP) for detecting increased arterial stiffness in general population.
Methods: A total of 515 asymptomatic patients without potential cause of liver disease who had liver fibroscan and cardio-ankle vascular index (CAVI) during their health check-up exams were included. A cut off of CAP ≥222 dB/m was used to define fatty liver and CAVI ≥ 8 for increased arterial stiffness.
Results: Both unadjusted and adjusted regression analyses showed significant association between fatty liver and increased arterial stiffness [unadjusted Odds ratio (OR) 1.896, 95% CI 1.305–2.754, p = .001 for CAP ≥ 222 dB/m alone]. With all traditional cardiovascular risk factors such as age, gender, body mass index, hypertension, diabetes mellitus, hypercholesterolemia and smoking adjusted, CAP ≥ 222 dB/m still showed significant association with increased arterial stiffness (OR 2.309, 95% CI 1.419–3.756, p = .001). The correlation between CAP-defined fatty liver and arterial stiffness was especially strong in subjects without diabetes (OR 2.959, 95% CI 1.709–5.122, p < 0.001).
Conclusion: CAP ≥ 222 dB/m is independently associated with increased arterial stiffness. As increased arterial stiffness is a surrogate and prognosticator for cardiovascular disease, surveillance using liver fibroscan may help screen and further stratify risk of patients.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a heterogeneous disease that includes steatosis, steatohepatitis and liver cirrhosis. NAFLD is becoming a very common disease in Korea, with a prevalence of 30% and the incidence still increasing [1,2] and is also becoming the most common cause of chronic liver disease worldwide. Not only NAFLD causes liver-related morbidity or mortality, but also increases extrahepatic manifestations; it is known to be one of the manifestations of metabolic syndrome and is subsequently related with poor cardiovascular outcome. Previous studies have demonstrated the associations between NAFLD and obesity, type II diabetes and dyslipidemia. Moreover, an association between the severity of NAFLD and the extent of increased cardiovascular risk has been shown [3–5]. Further, a significant association between NAFLD and increased arterial stiffness has been shown by measuring pulse wave velocity (PWV), augmentation index or ß-stiffness [6–8]. Arterial stiffness is one of the earliest detectable marker for structural and functional changes in blood vessel walls [9], and is established as a surrogate prognosticator of cardiovascular morbidity and mortality. However, the traditional methods have shown insurmountable limitations, since these methods were affected by blood pressure during measurement.

Cardio-ankle vascular index (CAVI) can be measured easily and is a highly reproducible index of arterial stiffness, which is superior to previous methods. CAVI is unaffected by blood pressure, reflects the stiffness of whole arterial segments from the aorta to the tibial artery, and involves PWV and blood pressure measurements. CAVI is associated with coronary atherosclerosis [10], LV dysfunction [11] and stroke [12]. As measured by CAVI, the risk for

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increased arterial stiffness increased by 42% with NAFLD suggesting that NAFLD is a risk factor for increased arterial stiffness [13]. The risk for arterial stiffness also correlated with the severity of NAFLD [13].

A recent longitudinal cohort study suggested that the amount of liver fibrosis was a primary determinant of patient outcomes [14]. Although liver biopsy is the gold standard method for diagnosing and assessing the severity of liver fibrosis, the invasiveness and possible sampling errors that arise from liver biopsies limit their use in clinical practice, especially in asymptomatic healthy subjects. Liver fibroscan has recently been suggested as an alternative method to measure liver steatosis quantitatively and noninvasively, and measurement of the controlled attenuation parameter (CAP) during transient elastography (TE) has shown high sensitivity for detecting low-grade steatosis, and good correlation with level of steatosis [15–17]. However, the association between arterial stiffness measured by CAVI and liver steatosis measured by liver fibroscan has not yet been studied in asymptomatic subjects. The aim of this study was to evaluate the association between the CAP value measured using liver fibroscan and increased arterial stiffness in a large number of apparently healthy subjects.

2. Patients and methods

2.1. Study population

A retrospective cohort of apparently healthy subjects who had both CAVI and liver fibroscan (Echosens, Paris, France) during health check-up exams at Healthcare System Gangnam Center, Seoul National University Hospital during January 2016 and December 2016 were enrolled in this study. Among 660 subjects who had both CAVI and liver fibroscan, eight subjects with known coronary artery disease and 137 subjects with potential cause of chronic liver disease were excluded; 111 with significant alcohol consumption as >20 g/day for males and >10 g/day for females [18], 21 with positive serum hepatitis B surface antigen, and 5 with positive serum hepatitis C antibody. Finally, 515 subjects were enrolled for analysis.

The study protocol followed the Declaration of Helsinki of 1975, as revised in 1983. This study was approved by the Institutional Review Board of Seoul National University Hospital (H-1611-098-809). Because the current study was performed with a retrospective design using a database and medical records, informed consent was waived by the board.

2.2. Measurement of anthropometric and laboratory parameters

Anthropometric and laboratory parameters were measured on the same day of the health check-up exam. The blood pressure, body weight, height and waist circumference were measured and body mass index (BMI) was calculated using height and body weight measured by a digital scale, according to the formula: BMI = weight (kg)/height (m^2). Waist circumference was measured at the midpoint between the lower costal margin and the iliac crest by a well-trained nurse.

Based on subject-recorded questionnaires and medications, each subject was categorized as a smoker or a non-smoker, the amount of alcohol each subject consumed was calculated, and comorbidities including hypertension, diabetes mellitus (DM), and hypercholesterolemia were evaluated. Subjects who were taking antihypertensive medications or whose blood pressure ≥ 140/90 mmHg were categorized as hypertensive. Subjects who were taking glucose-lowering agents or whose fasting blood sugar (FBS) ≥ 126 mg/dL or glycated hemoglobin (HbA1c) ≥ 6.5% were categorized as diabetic. Subjects who were taking lipid-lowering agents or whose total cholesterol ≥ 240 mg/dL or low density lipoprotein (LDL)-cholesterol ≥ 160 mg/dL were categorized as having hypercholesterolemia [19].

All blood tests were taken after at least 12 h of fasting, which included aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total cholesterol, triglyceride (TG), high-density lipoprotein (HDL) cholesterol, FBS, HbA1c. Measured LDL-cholesterol was used for analysis.

2.3. Quantitative assessment using CAP and liver stiffness

CAP and liver stiffness measurements (LSM) were obtained by fibroscan using an M probe. The procedure was performed by an experienced investigator who was blinded to the patients' clinical information. Liver fibroscan was performed on the right lobe through the intercostal spaces with the patient in the dorsal decubitus position and the right arm in maximal abduction [20]. CAP scores were expressed as median in dB/m values. LSM was expressed as the median kilopascals (kPa) value. LSM values were considered reliable if 10 valid measurements were obtained and the interquartile range/median of the measurements <0.3 regardless of LSM values or the interquartile range/median of the measurements >0.3 with the LSM median was <7.1 kPa [21]. All of the patients with 10 valid shots were included in the CAP analysis. In this study, CAP values of ≥222 dB/m were used to define NAFLD [22,23].

2.4. Assessment of arterial stiffness using CAVI

CAVI was measured with a VaSera VS-1000 (Fukuda Denshi Co. Ltd., Tokyo, Japan) as described previously [24–26]. Brachial pulse pressure was measured using an automatic cuff oscillometric device after 5-min of rest and with the subject seated. The average of two readings was used to determine systolic and diastolic pressures and pulse pressure. At supine position, cuffs were applied to both upper arms and ankles, and the measurement was performed after 10 min of rest. A phonocardiogram was placed at the right sternum border in the second intercostal space and electrocardiogram leads were attached to both wrists. CAVI was determined using the following equation;

$$\mathrm{CAVI} = \mathrm{a}[(2\rho/\Delta\mathrm{P}) \times \ln(\mathrm{Ps}/\mathrm{Pd}) \times \mathrm{PWV}^2] + \mathrm{b}$$

in which Ps and Pd are systolic and diastolic blood pressures, respectively, ΔP is Ps–Pd, ρ is blood density, and a and b are constants. The average value of the right and the left CAVI was used for analysis. The study subjects were grouped into two groups with CAVI ≥ 8 or CAVI < 8, and increased arterial stiffness was defined as CAVI ≥ 8.

2.5. Statistical analysis

Data were expressed as mean ± standard deviation or median (interquartile range) for continuous variables and as frequencies for categorical variables. Chi-square tests and Student's *t*-tests were used for categorical and continuous variables to compare the differences between different groups. To evaluate the parameters that affect increased arterial stiffness, univariate and multivariate logistic regression analysis were performed, and multiple models were evaluated to adjust possible confounders. All statistical analyses were performed using the Statistical Package for Social Science software (SPSS version 22), and a two-tailed p values <0.05 were considered to be statistically significant.

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