



Serum carcinoembryonic antigen level is associated with arterial stiffness in healthy Korean adult

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ABSTRACT

Background: Carcinoembryonic antigen (CEA), a widely used tumor marker, has been reported to be related with atherosclerosis and cardiovascular disease. However, little is known about the relationship between arterial stiffness and CEA level. We assessed whether serum CEA level is related with arterial stiffness by measuring brachial-ankle pulse wave velocity (ba-PWV) in healthy subjects.

Methods: Serum CEA level, ba-PWV and conventional risk factors were measured in 2909 subjects (1767 men and 1142 women) who underwent routine health checkup. We performed correlation, multiple linear regression and multiple logistic regression analyses to divide into quartiles according to CEA level.

Results: The mean values of ba-PWV increased gradually by CEA quartile. After correcting for significantly correlated variables, the ba-PWV was independently associated with CEA ($P < 0.001$). The odds ratios (95% CI) for high ba-PWV (>75th percentile; men: 1518 cm/s, women: 1487 cm/s) according to CEA quartile were 1.00 (Q1), 1.044 (0.659–1.652; Q2), 1.075 (0.688–1.681; Q3), and 1.595 (1.009–2.520; Q4) after adjusting for age, blood pressure, BMI, fasting glucose, heart rate, log hs-CRP, LDL-cholesterol, WBC count, alcohol intake, smoking and exercise in men ($P < 0.001$). The odds ratios (95% CIs) in women were 1.00 (Q1), 1.719 (0.971–3.032; Q2), 1.793 (1.019–3.156; Q3), and 2.330 (1.312–4.139; Q4) ($P < 0.001$) after adjusting for age, blood pressure, BMI, fasting glucose, heart rate, log hs-CRP, lipid profile, uric acid, WBC count, alcohol intake, smoking and exercise.

Conclusions: The CEA level is associated with arterial stiffness which measured by ba-PWV in healthy Korean men and women.

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1. Introduction

Carcinoembryonic antigen (CEA) is one of the most widely used tumor markers worldwide [1]. It is over expressed in adenocarcinomas in the colon and other organs including the pancreas, lung, prostate, urinary bladder, ovary, and breast. However, several non-malignant conditions, including acute and chronic inflammation and other inflammatory-related conditions such as aging and smoking are characterized by increased CEA concentrations [2]. Moreover, increased serum CEA concentrations at the high end of normal were associated with carotid atherosclerosis in Japanese men [3]. Recently, a study about elevated serum CEA level and metabolic syndrome in female Korean non-smokers was reported [4]. Although the function of CEA has not been fully known, several previous studies have revealed that CEA stimulates monocytes and macrophages to release pro-inflammatory cytokines [5] and eventually induce adhesion molecules on vascular endothelial cells [6]. This may lead to atherosclerosis, cardiovascular disease or metastasis of malignant cells [7,8].

Pulse wave velocity (PWV) is a simple, reproducible and noninvasive measurement that may be a valuable index of both arterial stiffness and atherosclerosis in large populations [9]. PWV has not only been reported to be a marker of vascular damage but also a significant predictor of cardiovascular events and mortality [10–12]. Also, the validity, reliability and reproducibility of this measurement have been confirmed suggesting that brachial-arterial PWV (ba-PWV) could be a useful tool for screening arterial stiffness in primary care settings [13]. Although slight elevation of serum CEA can be observed in apparently healthy individuals, little information is available on the possible association between serum CEA level and arterial stiffness in the general population. The present study was grounded in the hypothesis that CEA levels may profoundly affect arterial stiffness, represented as ba-PWV.

2. Methods

2.1. Study sample

The study sample consists of Korean men and women who visited the Gangnam Severance Hospital Health Promotion Center for a routine health checkup from May 2007 to August 2010. Among these participants, subjects with any missing covariate information were excluded.

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Patients with a history of anti-diabetic, anti-hypertensive, or lipid-lowering medications, malignancy, stroke, or cardiovascular disease such as coronary heart disease, peripheral artery disease, arrhythmia, congestive heart failure, or valvular heart disease and pregnant women were excluded, a total of 2909 men and women were enrolled. Subjects were divided into quartiles according to CEA level: Q1 (CEA < 1.3 ng/ml), Q2 (1.3 ng/ml ≤ CEA ≤ 1.8 ng/ml), Q3 (1.9 ng/ml ≤ CEA ≤ 2.6 ng/ml), and Q4 (2.7 ng/ml < CEA) in men; Q1 (CEA < 1.0 ng/ml), Q2 (1.0 ng/ml ≤ CEA ≤ 1.3 ng/ml), Q3 (1.4 ng/ml ≤ CEA ≤ 1.9 ng/ml), and Q4 (2.0 ng/ml < CEA) in women.

The Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine approved this study and informed consent was obtained from each participant.

2.2. Measurements

Blood pressure and resting heart rate (RHR) were measured after more than 5 min of rest. Anthropometric measurements were used to calculate body mass index (BMI). To reduce inter-observer variation in measurements, one researcher gathered all anthropometric parameters throughout the study. A questionnaire was used to obtain information about a participant's medical history and lifestyle, including exercise, smoking habits, and alcohol consumption. A never smoker was defined as someone who had smoked < 100 cigarettes during their lifetime. A smoker was defined as someone who had smoked > 100 cigarettes. Among the latter group, those who affirmatively answered the question "Do you currently smoke?" were defined as current smokers, whereas those who answered in the negative were defined as former smokers. In this study, smokers were defined as current smokers. Regular exercise was defined as doing physical activity > 3 times a week for > 30 min. Alcohol intake was defined as drinking regularly more than one time a week. Subjects were instructed to refrain from alcohol the day before testing as well as smoking, coffee, tea, and pain medication on the day of measurement.

After an overnight fast, serum glucose, total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol levels were measured via enzymatic procedures using an chemistry analyzer (ADVIA 1650, Siemens Healthcare, Tarrytown, NY). Low-density lipoprotein (LDL)-cholesterol was calculated by the Friedewald formula [14].

Table 1
Clinical and metabolic characteristics of the study participants.

	Male (n = 1767)	Female (n = 1142)
Age (y)	53.1 (9.6)	53.1 (17.4)
Systolic blood pressure (mm Hg)	126.8 (16.1)	120.3 (18.4)
Diastolic blood pressure (mm Hg)	79.1 (9.4)	73.9 (10.7)
BMI (kg/m ²)	24.6 (2.8)	22.5 (2.9)
Fasting plasma glucose (mg/dl)	100.4 (21.8)	93.0 (18.1)
Heart rate (beats/min)	73.5 (11.4)	74.9 (11.3)
WBC (10 ³ /μl)	6.27 (1.77)	5.44 (1.56)
Hs-CRP (mg/l)	1.8 (3.6)	1.3 (2.6)
Uric acid (mg/dl)	5.9 (1.2)	4.3 (0.9)
Total cholesterol (mg/dl)	191.5 (35.7)	196.5 (34.7)
LDL-cholesterol (mg/dl)	130.3 (36.7)	127.2 (35.2)
HDL-cholesterol (mg/dl)	47.1 (11.2)	56.6 (13.2)
Triglyceride (mg/dl)	135.8 (81.1)	127.2 (35.2)
CEA (ng/ml)	2.1 (1.3)	1.5 (0.9)
Ba-PWV (cm/s)	1420.4 (228.8)	1378.9 (258.9)
Alcohol intake, n (%)	876 (49.6)	544 (47.4)
Current smoker, n (%)	602 (34.1)	91 (7.9)
Former smoker, n (%)	813 (46.0)	82 (7.1)
Nonsmoker, n (%)	352 (19.9)	974 (84.9)
Regular exercise, n (%)	640 (36.2)	529 (46.1)

Numerical data are presented as mean (±SD). Regular exercise was defined as physical activity ≥ 3 days/week for > 30 min. Alcohol intake was defined as drinking regularly ≥ 1 days/week.

Note: BMI = body mass index; WBC = white blood cell count; Hs-CRP = high-sensitivity C-reactive protein; CEA = carcinoembryonic antigen; ba-PWV = brachial-ankle pulse wave velocity.

High-sensitivity C-reactive protein (hs-CRP) was measured using a latex-enhanced immunoturbidimetric assay in an ADVIA 1650 (Siemens). CEA level was measured via CLIA method using Unicel DXI 800 analyzer (Beckman-Coulter, Chaska, MN). White blood cell count (WBC) was measured using ADVIA 2120i (Siemens).

2.3. PWV measurement

Ba-PWV was measured using a volume plethysmographic instrument (PWV/ABI; Colin Co, Komaki, Japan), which recorded a phonocardiogram, electrocardiogram, volume pulse form, and arterial blood pressure at the left and the right brachial arteries and ankles. The ba-PWV was calculated using time-phase analysis between the right brachial artery pressure and the volume waveforms at both ankles. The distance between the right brachium and the ankle was estimated based on the subject's height. We used the mean ba-PWV in the analyses. Both ba-PWV values were measured after allowing the patient to rest in the supine position for at least 5 min in an air-conditioned room (24–26 °C).

2.4. Statistical analyses

All analyses were performed using SPSS for Windows (ver 18.0; SPSS Inc., Chicago, IL). Mean values of clinical characteristics were shown between men and women. All data are presented as mean value (SD) and categorical variables were presented as frequencies and percentages. Because of the skewed distribution of hs-CRP and triglyceride, this parameter was logarithmically transformed.

Pearson's correlation analysis was performed to evaluate the relationships of clinical parameters to ba-PWV. Multiple linear regression analysis with a stepwise forward selection procedure was performed to identify any independent associations between ba-PWV and CEA levels. A high ba-PWV group (> 75th percentile) was defined as > 1518 cm/s in men and 1487 cm/s in women. The odds ratios (95% confidence intervals [CIs]) for high ba-PWV were calculated using a multivariable logistic regression analysis after adjusting for confounding factors. A P < 0.05 was considered statistically significant.

3. Results

The clinical and metabolic characteristics of males (n = 1767) and females (n = 1142) enrolled in this study are shown in Table 1. Mean

Table 2
Pearson's correlations between ba-PWV and various parameters.

	Pulse wave velocity			
	Men		Women	
	r	P-value	r	P-value
CEA (ng/ml)	0.132	<0.001	0.224	<0.001
Age (yrs)	0.514	<0.001	0.309	<0.001
Systolic blood pressure (mm Hg)	0.347	<0.001	0.562	<0.001
Diastolic blood pressure (mm Hg)	0.294	<0.001	0.537	<0.001
BMI (kg/m ²)	0.088	<0.001	0.187	<0.001
Fasting plasma glucose (mg/dl)	0.226	<0.001	0.378	<0.001
Heart rate (beats/min)	0.164	<0.001	0.172	<0.001
WBC (10 ³ /μl)	0.041	0.093	0.205	<0.001
Log(hs-CRP) (mg/l)	0.115	<0.001	0.263	<0.001
Uric acid (mg/dl)	0.037	NS	0.200	<0.001
Total cholesterol (mg/dl)	0.038	NS	0.184	<0.001
LDL-cholesterol (mg/dl)	0.058	0.016	0.198	<0.001
HDL-cholesterol (mg/dl)	-0.019	NS	-0.179	<0.001
Log(triglyceride) (mg/dl)	0.014	NS	0.244	<0.001
Alcohol intake	-0.119	<0.001	-0.179	<0.001
Smoking	0.022	NS	0.074	0.018
Regular exercise	-0.012	NS	-0.009	NS

Coefficients (r) and P-values were calculated using a Pearson's correlation model. Smoking was defined as current smoking. Note: CEA = carcinoembryonic antigen; ba-PWV = brachial-ankle pulse wave velocity.

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