The Correlation of Age and Fasting Blood Sugar with Cardio-Ankle Vascular Index in Southern Thai Healthy Volunteers

Kittinutt Chaiyawong, Pornchai Sathirapanya**, Siriphun Hiranyachattada**

Abstract

Arterial stiffness is associated with advancing age and the accumulation of atherosclerotic plaque which may lead to an increase in cardiovascular risk events such as myocardial infarction or stroke. It can be predicted by using cardio-ankle vascular index (CAVI) and high sensitivity C-reactive protein (hsCRP), which is an inflamatory marker of subclinical atherosclerosis. This study aimed to measure the CAVI in southern Thai volunteers who has no history of cardiovascular diseases and to find the correlations between CAVI and age, fasting blood sugar (FBS), blood lipid profile or hsCRP**.** CAVI of the subjects were determined using sphygmomanometer (VaSera VS-1500N) based on the equation, $CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2\}+b$. Regression analysis revealed a significant positive correlation between 1) CAVI and age ($CAVI = 4.94 + 0.05*AGE$; $R = 0.66$, $P < 0.001$) and 2) CAVI and FBS ($CAVI = 4.96 + 0.02*FBS$; $R = 0.35$, $P < 0.05$). There was no significant correlation between CAVI and serum lipid profile or hsCRP. Logistic regression analysis also suggested the significant relation between two cardiovascular risk factors, gender and age, and the high CAVI of > 8.0.

J Physiol Biomed Sci. 2016; 29(1): 12-17

Keywords: *Arterial stiffness, cardio-ankle vascular index, CAVI, fasting blood sugar, high sensitivity C-reactive protein*

Introduction

Arterial stiffness, a predictor of atherosclerosis, can be assessed by various noninvasive methods including the measurement of pulse wave velocity (PWV) and cardio-ankle vascular index (CAVI). The PWV can be determined simply by recording the arterial pulse waves at the proximal artery such as carotid-femoral PWV (cfPWV), brachial-ankle PWV (baPWV), and femoral-tibial PWV (ftPWV). Noninvasive detection of arterial pulse waves can be achieved by using pressure-sensitive transducer[1] or Doppler ultrasound.[2] However, the validity and reproducibility in using the PWV measurement to predict the arterial distensibility have been concerned and recently reviewed.[3] For example, the cfPWV can be used to determine aortic arterial stiffness since it is well correlated with atherosclerosis.[4] On the other hand, the use of baPWV in reflecting the vascular damage is limited due to the effect by blood pressure at the time of measurement.[5] Moreover, the aortic PWV as assessed by using Doppler flow recording is influenced by certain factors such as antihypertensive agents or weight loss.[6]

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Received 17 May 2016, Accepted 11 July 2016

Cardio-ankle vascular index (CAVI) is a novel blood pressure-independent arterial wall stiffness parameter which has clinical significance.[7,8,9] CAVI is determined by using an electrocardiogram (ECG), phonocardiogram (PCG), and PWV from the starting point of the aorta (from the heart) to the ankle. Several studies have shown the importance of CAVI and its clinical significance in hypertension[6], diabetes mellitus (DM),[9] coronary artery disease (CAD), [10,11] and carotid atherosclerosis.[12] The CAVI determination has also been reported to have a good reproducibility in healthy Japanese subjects and patients.[7,8] These indicate the effectiveness of CAVI for routine examination in large scale subjects. In addition, CAVI might be another useful predictor of coronary atherosclerosis in subjects with a risk factor for cardiovascular disease.[13]

The majority of cardiovascular diseases (CVD) are caused by various risk factors, such as high blood pressure, high blood cholesterol, obesity, diabetes mellitus, and advancing age. Arterial stiffness which is associated with advancing age can lead to an increase in cardiovascular risk events, such as myocardial infarction or stroke. Besides, glycemic and lipid profile have also been used as risk factors for CVD. In addition, high sensitivity C-reactive protein (hsCRP) has been implemented as a marker of subclinical atherosclerosis.[14]

In Thailand, the traditional risk score (RAMA-EGAT) has been used to predict the occurrence of CVD including CAD.[15,16] The modified RAMA-EGAT score, by addition of CAVI, has shown to improve the diagnostic accuracy of CAD.[17] Several

studies have demonstrated the correlation between CAVI and other atherosclerosis risk factors in the Japanese; however, fewer data are available for the Thai population.

The objective of this study was to investigate the correlation between CAVI and age, arterial blood pressure, glycemic state, lipid profile or hsCRP in southern Thai healthy volunteers who has no history of CVD.

Materials and Methods

Subjects

Two hundred and one healthy Thai voluteers were enrolled in this study. Their ages ranged from 30-69 years. All subjects attended an annual health checkup at Songklanagarind Hospital between August 2014-April 2015. Among these subjects, 114 persons were excluded due to the following conditions: medical history of cardiovascular diseases such as hypertension, stroke or peripheral arterial diseases, diabetes mellitus, current illness, tissue injury, infection or other general inflammation, and taking medications for diabetes, hypertension, and dyslipidemia. The final analytical sample size was confined to 87 subjects. The study protocol was approved by the Human Research Ethics Committee, Faculty of Medicine, Prince of Songkla University (REC. 57-0163-19-9).

All subjects were then informed regarding the details of study protocol, before signing the consent forms to participate in this research and completed self-reported questionnaires which included gender, age, height, body weight, waist circumference and body mass index (BMI). Determination of CAVI was performed in the same month of their annual health checkup. Blood sampling for chemical analysis were carried out at Songklanagarind Hospital after an overnight fasting.

Calculated sample of population

In order to obtain the relation between CAVI and cardiovascular risk, the sample size was calculated using the following formula:

$$n = \left[\frac{(Z_{\alpha/2} + Z_{\beta})}{[F(Z_1)]}\right]^2 + 3$$

$$F(Z) = \frac{ln\left[\frac{1+r}{1-r}\right]}{2}$$

Where $Z_\alpha = 1.96$; when α was 0.05

$Z_\beta = 0.842$; when β was 0.2

r = 0.3; correlation coefficient obtained from cardio-ankle vascular index and cardiovascular risk.

Therefore,

$$n = \left[\frac{(1.96 + 0.842)}{[F(Z_1)]}\right]^2 + 3$$

$$n = 85$$

Experimental protocol for CAVI determination

CAVI was determined using a similar technique as the measurement of baPWV by employing a VaSera VS-1500N vascular screening system (Fukuda Denshi Co., Tokyo, Japan) which is a movable machine with print-out function. All subjects' CAVIs were measured in supine position following an advice of relaxation as much as possible. Arterial blood pressure was detected at both arms and ankles simultaneously using standard pressure cuffs. A microphone for phonocardiogram was placed on the sternum. ECG and blood pressure waveforms of the brachial and ankle artery were recorded at the same time. CAVI were automatically calculated by a CAVI-Vasera VS 1500N, which was based on the formula;

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

where, Ps is systolic blood pressure, Pd is diastolic blood pressure, PWV is pulse wave velocity from the origin of the aorta to the junction of the tibial artery with the femoral artery, ΔP is Ps-Pd, ρ is blood density, and a and b are constants.

In this study, the CAVIs of both sides from each subject were averaged and used for the correlation and regression analyses. The calculated CAVI can be used to indicate the total stiffness of the aorta, femoral artery, and tibial artery, which theoretically were not affected by blood pressure as previously reported.[7]

Measurement of blood samples

Blood samples were collected from subjects after an overnight fasting between 8-12 hours for determination of fasting blood sugar (FBS), serum triglyceride, total cholesterol, low density lipoprotein (LDL), and high density lipoprotein (HDL), using an automated analyzer (Modular P800, Roche Diagnostics GmbH, Mannheim, Germany). hsCRP was determined by particle enhanced immunoturbidimetric assay, in which human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies using turbidimeter (cobas c 501, Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analyses

The SPSS software package (V.17.0) was used for the statistical analyses. All data were expressed as mean ± standard deviation (SD). Sample *t* test was used to compare the general characteristics of the study population for both sexes. ANOVA with multiple comparisons using Tukey *post hoc* test was used to compare the mean between the subgroups. A *P* value of less than 0.05 was considered statistically significant.

Simple linear regression analysis was used to find the correlation between CAVI and FBS, lipid profile, hsCRP or other clinical parameters. Stepwise multiple regression analysis was applied to the data to examine the independent determinants of CAVI.

Table 1 Data collected from 87 southern Thai volunteers who had no history of cardiovascular disease, with comparisons between male and female subjects.

Parameters	Both sexes	Male	Female	*P* value
Number of subjects	87	29	58	
Age (years)	49.6 ± 10.2	49.6 ± 11.0	49.7 ± 10.8	0.87
Height (cm)	159.9 ± 7.5	167 ± 5.9	156.3 ± 5.3	0.80
Weight (kg)	60.0 ± 10.8	66.8 ± 9.2	56.5 ± 9.9	0.82
BMI (kg/m^2)	23.4 ± 3.6	23.9 ± 3.0	23.1 ± 3.8	0.40
Waist circumference (cm)	80.4 ± 9.4	84.9 ± 7.9	78.2 ± 9.4	0.46
SBP (mmHg)	118 ± 12	118 ± 10	117 ± 12	0.13
DSP(mmHg)	73 ± 8	74 ± 7	72 ± 8	0.54
MABP (mmHg)	89 ± 8	89 ±7	88 ± 8	0.11
HR (beats/minute)	70 ± 10	68 ± 9	71 ± 11	0.63
Total cholesterol (mg/dl)	210 ± 39	208 ± 39	217 ± 39	0.76
Triglyceride (mg/dl)	117 ± 74	135± 101	108 ± 53*	0.007
LDL cholesterol (mg/dl)	142 ± 38	142 ± 38	141 ± 38	0.80
HDL cholesterol (mg/dl)	62 ± 16	57 ± 17	64 ± 16	0.93
FBS (mg/dl)	99 ± 14	102 ± 12	98 ± 15	0.67
hsCRP (mg/l)	1.5 ± 1.6	1.3 ± 1.2	1.5 ± 1.8	0.99
CAVI	7.4 ± 0.8	7.6 ± 0.8	7.3 ± 0.7	0.57

All parameters are expressed as mean ± SD. *Significant difference at $P < 0.05$ (*t* test).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure; HR, heart rate; CAVI, cardio-ankle vascular index; LDL, low density lipoprotein, HDL, high density lipoprotein; FBS, fasting blood sugar; hsCRP, high sensitivity C-reactive protein.

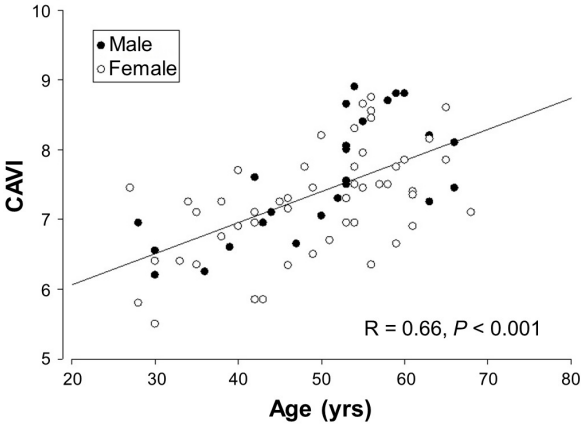

Figure 1 Correlation between cardio-ankle vascular index (CAVI) and age in 87 subjects (male = 29, female = 58). The regression line analysis was obtained from data for both sexes. Least squares fit for both sexes, CAVI = 4.94 + (0.05 * Age), $R^2 = 0.43$, $P < 0.001$.

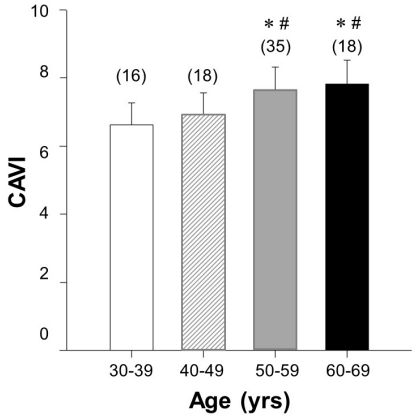

Figure 2 Comparing average CAVI among 4 groups of subjects with 10 year age interval. *, # ($P < 0.05$) when compared to 30-39 years and 40-49 years, respectively (ANOVA with Tukey *post hoc* test).

Results

Data collected from 87 subjects (58 women, 29 men) in southern Thailand who had no history of cardiovascular disease were analyzed as shown in Table 1. The overall mean age (± SD) was 49.6 ± 10.2 years (range 30-70 years), with 49.6 ± 11.0 years for males and 49.7 ± 10.8 years for females. There was no significant difference between the mean age of both sexes ($P = 0.873$). The mean ± SD of other parameters (both sexes) were: height, 159.9 ± 7.5 cm; weight, 60.0 ± 10.8 kg; BMI, 23.4 ± 3.6 kg/m^2; waist circumference, 80.4 ± 9.4 cm; SBP, 118 ± 12 mmHg; DBP, 73 ± 8 mmHg; MABP, 89 ± 8 mmHg; HR, 70 ± 10 beats/min; total cholesterol, 210 ± 39 mg/dl; triglyceride, 117 ± 74 mg/dl; LDL, 142 ± 38 mg/dl; HDL, 62 ± 16 mg/dl; FBS, 99 ± 14 mg/dl; hsCRP, 1.4 ± 1.6 mg/l and CAVI, 7.4 ± 0.8. The triglyceride levels of females were significantly lower than those of the male group ($P = 0.007$).

Table 2 Correlation between cardio-ankle vascular index (CAVI) and either general or clinical parameters.

	R	*P* value
Age (years)	0.660	0.000
Height (cm)	-0.111	0.153
Weight (kg)	-0.068	0.266
BMI (kg/m^2)	-0.016	0.443
Waist circumference (cm)	0.103	0.172
SBP (mmHg)	0.184	0.087
DBP (mmHg)	0.213	0.048
MABP (mmHg)	0.228	0.003
HR (beats/minute)	-0.070	0.259
Total cholesterol (mg/dl)	0.067	0.537
Triglyceride (mg/dl)	-0.063	0.280
LDL cholesterol (mg/dl)	-0.081	0.228
HDL cholesterol (mg/dl)	0.059	0.292
FBS (mg/dl)	0.323	0.001
hsCRP (mg/l)	0.083	0.222

The total number of both sexes is 87.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure; HR, heart rate; LDL, low density lipoprotein, HDL, high density lipoprotein; FBS, fasting blood sugar and hsCRP, high sensitivity C-reactive protein .

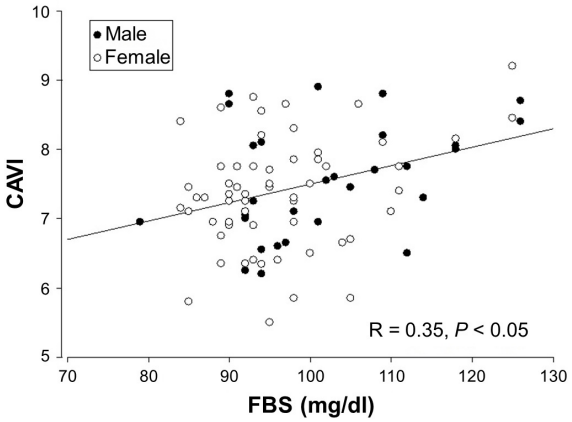

Figure 3 Correlation between cardio-ankle vascular index (CAVI) and fasting blood sugar (FBS) in all 87 subjects (29 males, 58 females). The regression line analysis was obtained from data for both sexes. Least squares fit for both sexes, CAVI = 4.80 + (0.02*FBS), R^2 = 0.117, P < 0.001.

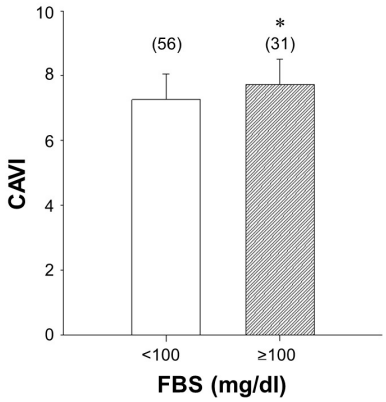

Figure 4 Comparing mean of CAVI between two subgroups of subjects who has fasting blood sugar (FBS) lower (<) and higher (≥) than 100 mg/dl. * P < 0.05 when compared to FBS <100 mg/dl (*t* test).

Table 3 The relationships between cardiovascular risk factors and high CAVI (> 8.0) using logistic regression analysis (forward stepwise).

Risk factor	CAVI > 8					
	β	S.E.	Wald	df	Sig.	Odds ratio
Gender	1.453	.628	5.350	1	0.021	4.278 (for male)
Age	0.160	.042	14.242	1	0.000	1.174 (30-69 yrs)

Calculation for the odds ratio was derived from the parameters including age, gender, height, weight, BMI, systolic, diastolic and mean arterial blood pressure, heart rate, total cholesterol, triglyceride, LDL and HDL cholesterol, fasting blood sugar and hsCRP. Only the gender (male) and age (30-60 years old) are found significant. β, the standardized regression coefficient for constant; S.E., standard error; Wald, Wald chi-square test; df, the degree of freedom; Sig., Significance; Odd ratio was taken from the exponentiation β coefficient.

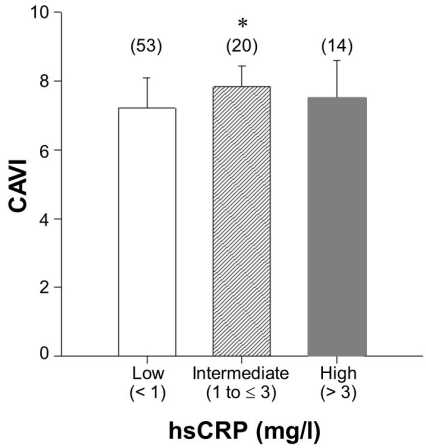

Figure 5 Comparing mean of CAVI among three subgroups of subjects with hsCRP less than 1 mg/l (Low, <1), between 1 to 3 mg/l (Internediate, 1 to ≤ 3) and more than 3 mg/l (High, > 3). * P < 0.05 when compare to hsCRP < 1 mg/l (ANOVA with Tukey *post hoc* test).

In this study, CAVI showed a positive correlation with age (P < 0.001), with a regression coefficient, R = 0.66. With this regression analysis, the value of CAVI increased approximately 0.05 for every year of an increasing age (Figure 1). Comparison of CAVI mean among 4 subgroups of subjects, with 10 years age interval, showed significantly higher CAVI in both 50-59 and 60-69 years old groups, when compared to either of 30-39 or 40-49 years old group (Figure 2).

CAVI showed a significantly positive correlation with FBS (P = 0.001, R = 0.35; Figure 3). According to the regression analysis, it was found that CAVI increased approximately 0.02 for every 1 mg/dl increase in FBS. Further subgroup analysis of FBS levels revealed that subjects with FBS ≥ 100 mg/dl had significantly higher CAVI (7.72 ± 0.78) when compared to those with FBS < 100 mg/dl (7.26 ± 0.78; Figure 4).

The correlation between CAVI and the general or clinical parameters is shown in Table 2. It was found that CAVI significantly correlated with only age, DBP, MABP and FBS (P < 0.05). However, CAVI had no significant correlation with the other measured parameters including weight, height, BMI, waist circumference, SBP, HR, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, and hsCRP.

The hsCRP levels of 87 subjects were further divided into 3 subgroups according to the risk levels for cardiovascular diseases: low group, hsCRP < 1 mg/l; intermediate group, 1 mg/l < hsCRP < 3 mg/l; and high group, hsCRP > 3 mg/l. It was found that the intermediate group had significantly higher CAVI (7.55 ± 0.64) when compared to the low group (7.31 ± 0.80, P < 0.05; Figure 5). Logistic regression analysis revealed the relationships between cardiovascular risk and high CAVI (> 8.0) as shown in Table 3. For the whole subjects studied, the odds ratio of the sex (male) and age for a high CAVI was 1.45 (95% CI, 1.248 to 14.659) and 0.160 (95% CI, 1.080 to 1.275), respectively. According to this analysis, the overall predicted percentage of the

arterial stiffness yielded approximately 80% accuracy by this model.

Discussion

In this study, we initially assumed that the age, arterial blood pressure, glycemic state, lipid profile, and hsCRP of our subjects might correlate with arterial stiffness, according to the predefined CAVI criterion as previously reviewed.[18] However, we found that among the southern Thai subjects who had no history of cardiovascular disease, their calculated CAVI correlated strongly with age (both sexes). According to the regression analysis of these correlations, it could be predicted that CAVI would increase approximately 0.05 for every year of increasing age, even though the linear equations of both sexes were not quite similar. For men, CAVI = 4.77 + (0.058*age) and for woman, CAVI = 5.00 + (0.047*age). However, this information was in accordance with a previous study in 32,627 Japanese without cardiovascular risks who received annual health checkup. CAVI of the Japanese men was higher than women group in every increasing five years of age. The correlations of CAVI and age were found to be CAVI = 5.43 + (0.053*age) for men and CAVI = 5.34 + (0.049* age) for women.[18]

Age is the one of several factors that affect CAVI. The increase in arterial stiffness that occurs with age results from progressive vascular wall elastic fiber and collagen degeneration[19] and calcification.[20] The advanced age is also related to the changes in systolic and diastolic blood pressure due to the changes in the stiffness of the large arteries, such as the aorta and its major branches. In this study, we found that CAVI showed a significantly positive correlation with DBP and MABP, suggesting an increase in total peripheral resistance (TPR) might play an important role in age-related CAVI determination. The deterioration of arterial elasticity in aging may cause an increase in TPR and hence DBP and MABP.

The cutoff point of CAVI for the presence of coronary stenosis in the patients was reported to be 8.91.[10] Since our subjects were classified in low and intermediate risk population, the CAVI > 8.0 was chosen for the stepwise multiple regression analysis. As shown in Table 3, the significant relationships between cardiovascular risk factors, both gender and age, and a high CAVI (> 8.0) were observed. Thus, it is likely that CAVI can be used to reflect the progression of arterial stiffness with advancing age and the degree of stiffness is much higher in the male than female.

CAVI has been reported to be high in diabetic patients and was suggested as a useful indicator of early arteriosclerosis;[8] insulin treatment can significantly lower CAVI.[21,22] In this study, CAVI was positively correlated with FBS (Figure 3) but neither correlated with lipid profile nor hsCRP. When the subject FBS values were divided into two subgroups (< 100 mg/dl, n = 56, and ≥ 100 mg/dl, n = 31), the CAVI of those ≥ 100 mg/dl subgroup was significantly higher than the < 100 mg/dl subgroup (Figure 4). This may indicate an influent stressor on the arterial wall, and signify a lower FBS target for DM control by lowering the fasting blood glucose.

Inflammatory diseases of the arterial wall have been acknowledged to be associated with increased atherosclerosis.[7] The association between hsCRP with arterial stiffness was also studied in our subjects. In this study, CAVI was not significantly correlated with hsCRP levels which may be due to the limited number of the subjects affecting the variability of this study. However, the intermediate level hsCRP (1-3 mg/l) group had higher CAVI when compared to the low level hsCRP (< 1 mg/l) group, and the high level hsCRP (> 3 mg/l) group showed a nonsignificant difference when compared to the other two groups (Figure 5). Therefore, the correlation between hsCRP levels and CAVI in prediction of subclinical atherosclerosis needs a further large sample-size study.

There was no significant correlation between CAVI and blood lipid profile, triglyceride, and total cholesterol in our subjects who had no history of cardiovascular disease. A previous study reported that CAVI and hyperlipidemia were not intimately connected because it may not immediately increase arterial wall stiffness[18] even though a research reported that CAVI was related to the LDL-cholesterol level and also the total cholesterol/HDL-cholesterol ratio.[23] However, the mean blood triglyceride level in male group in this study was significantly higher than those of the female group, while other lipid levels and cholesterol were not different. The effect of gender on blood lipids, including triglyceride in healthy subjects, that was stronger in men than women at the same age was earlier reported.[24] The female hormone, estrogen, may exert a positive effect on resting and exercise fat metabolism[25] and this would result partly in a different blood lipid profile such as triglyceride of this study. Nevertheless, the high blood lipid levels and high ratio of TG-HDL constituted a significant risk for increased arterial stiffness and atherosclerosis especially in diabetes as evaluated by CAVI.[26]

Conclusion

In the southern Thai healthy subjects of this study, age is the most significant factor that affects arterial stiffness and FBS has positive correlation with arterial stiffness as assessed by CAVI. There is no correlation between an inflammatory marker (hsCRP), blood cholesterol, triglyceride, HDL or LDL and CAVI. Females have a tendency to have less arterial stiffness than male subjects at the same age, which may be due to the higher blood estrogen level particularly before menopause. In addition, CAVI is one of the noninvasive, simple, reproducible

and sensitive techniques in evaluation of arterial stiffness.

Acknowledgments

This work was supported by Faculty of Graduate School (Financial Support for Thesis), Prince of Songkla University (PSU), Hatyai, Songkhla, Thailand. We are grateful to Dr. Chanon Kongkamol, Department of Community Medicine, for his assistance in statistical analyses and Ms Panudda Musigavon, Clinical Chemistry Unit, Department of Pathology Faculty of Medicine, PSU for blood chemistry analyses.

Conflict of Interest

None to declare.

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