Original Article

Songklanagarind Medical Journal

ความสัมพันธ์เชิงบวกระหว่างการสูบบุหรี่และดัชนีหลอดเลือดแดงแข็งในผู้ใหญ่ที่ไม่มีโรคประจำตัว

Positive Relationship between Smoking and the Arterial Stiffness Index in Adults without Underlying Diseases

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Songkla Med J 2017;35(2):159-168

บทคัดย่อ:

วัตถุประสงค์: การสูบบุหรี่เป็นหนึ่งในปัจจัยเสี่ยงที่สำคัญของการเกิดโรคต่างๆ รวมถึงโรคหลอดเลือดแดงส่วนปลาย ซึ่งเป็นรูปแบบหนึ่งของโรคหัวใจและหลอดเลือดที่ส่งผลต่อหลอดเลือด ทำให้เกิดการแข็งและการตีบของหลอดเลือด เทคนิคการตรวจหาค่า ankle-brachial index (ABI) และ ค่า cardio ankle vascular index (CAVI) ซึ่งเป็นการตรวจที่ไม่รุกราน ถูกนำมาใช้ประเมินภาวะหลอดแดงอุดตันและหลอดเลือดแดงแข็งตามลำดับ ดังนั้นงานวิจัยนี้จึงมีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ของการสูบบุหรี่และภาวะของหลอดเลือดแดงส่วนปลาย โดยประเมินจากค่า ABI และ CAVI ของผู้ที่สูบบุหรี่และไม่สูบบุหรี่

วัสดุและวิธีการ: อาสาสมัครที่ไม่มีโรคประจำตัวเข้าร่วมการวิจัยทั้งหมด 141 คน แบ่งเป็นผู้ที่สูบบุหรี่ 49 คน และผู้ที่ไม่สูบบุหรี่ 92 คน อาสาสมัครทั้งหมดถูกสัมภาษณ์เพื่อรวบรวมข้อมูลด้านประวัติส่วนตัว ประวัติสุขภาพ และพฤติกรรมการสูบุหรี่ จากนั้นทำการประเมินหลอดเลือดส่วนปลายโดยวัดค่า ABI และ CAVI

ผลการศึกษา: พบว่าค่า CAVI ของผู้ที่สูบบุหรี่ (7.88±1.26) มีความแตกต่างกับผู้ที่ไม่สูบบุหรี่ (7.17±0.94) อย่างมีนัยสำคัญทางสถิติที่ p-value<0.001 เมื่อใช้สถิติการวิเคราะห์พหุตัวแปร พบว่าอายุและการสูบบุหรี่เป็นปัจจัยสำคัญที่มีผลต่อค่า CAVI นอกจากนี้ยังพบความสัมพันธ์เชิงบวกระหว่างค่า CAVI และจำนวนบุหรี่ที่สูบต่อวัน (r=0.31) และระยะเวลาในการสูบ (r=0.42) อย่างมีนัยสำคัญทางสถิติ ที่ p-value<0.001 แต่อย่างไรก็ตาม ค่า ABI ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในกลุ่มผู้ที่สูบบุหรี่และไม่สูบบุหรี่

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สรุป: ผลการศึกษาแสดงให้เห็นว่าอายุและการสูบบุหรี่เป็นปัจจัยสำคัญที่มีผลต่อค่า CAVI นอกจากนี้ยังพบว่าจำนวนมวนของการสูบบุหรี่ต่อวันและระยะเวลาการของการสูบบุหรี่มีความสัมพันธ์เชิงบวกกับค่า CAVI

คำสำคัญ: การสูบบุหรี่, ค่าดัชนีโอแองเกิลวาสคิวลาอินเด็กซ์, ค่าแองเกิลเบรเคียลอินเด็กซ์, หลอดเลือดแดงแข็ง, หลอดเลือดแดงอุดตัน

Abstract:

Objective: Smoking is a leading risk factor for various diseases including peripheral arterial disease (PAD). PAD is a form of cardiovascular disease that affects the blood vessels, resulting in vascular stiffness and occlusion. The ankle-brachial index (ABI) and cardio-ankle vascular index (CAVI) are non-invasive techniques for detection of vascular occlusion and stiffness, respectively. To determine the association between cigarette smoking and peripheral arterial conditions, the ABI and CAVI of smokers and non-smokers were investigated.

Material and Method: One hundred and forty one middle-aged participants without underlying diseases were enrolled, 49 smokers and 92 non-smokers. A questionnaire was developed to collect the demographic information, medical history, and smoking behaviours of the participants, and their ABI and CAVI were measured.

Results: Our results showed that the CAVI values of smokers (7.88±1.26) were significantly differed from those of non-smokers (7.17±0.94) at p-value <0.001. In addition, age and cigarette smoking were independent factors significantly related to the CAVI values by a multivariate analysis. Likewise, we found a positive relationship between the CAVI values and the number of cigarettes smoked per day (r=0.31) and the length of smoking duration (r=0.42) at p-value <0.001. However, the ABI values between smokers and non-smokers were not different.

Conclusion: This study demonstrated that age and smoking were significantly related to CAVI, and a greater number of cigarettes smoked per day and longer smoking duration had positive relationships to CAVI values.

Keywords: ankle-brachial index, arterial occlusion, arterial stiffness, cardio-ankle vascular index, cigarette smoking

Introduction

Cigarette dependence is still a global public health issue. About six million people per year die from smoking-related diseases.[1] In Thailand, although the overall percentage of smokers has gradually decreased over the last twenty years, smoking was the second-leading risk factor accounting for serious diseases among Thai males in 2015.[2] There are various smoking-related complications including chronic obstructive pulmonary disease (COPD), lung cancer, and cardiovascular diseases.[3] Smoking is also a prominent risk factor for peripheral arterial disease (PAD).[4] PAD is a cardiovascular disease that affects blood vessels throughout the body except those supplying blood to the heart. The affected blood vessels stiffen and narrow from a slow build-up of lipid plaque in the sub-endothelial layer which is called arteriosclerosis. In PAD, the most common lesions occur in the lower extremities. The narrowed-blood vessels lead to insufficient blood flow to the legs resulting in intermittent claudication, rest pain, and non-healing wounds and tissue gangrene.[5]

There are many diagnostic methods for PAD. Computed tomographic angiography, magnetic resonance angiography and contrast-enhanced angiography can be used to diagnose PAD. However, these techniques are invasive to the patients and are also complex and expensive. Non-invasive techniques that are more simple and inexpensive with diagnostic accuracy for vascular stenosis have been widely used. The ankle-brachial index (ABI) is the ratio of systolic blood pressure of the lower and upper extremities.[6] It has been reported that low values of ABI (≤0.9) have a strong association with serious stenosis of PAD (≥50.0%) with a specificity of 86.0% and a sensitivity of 75.0%.[7] The cardio-ankle vascular index (CAVI), an arterial stiffness index, is a novel diagnostic parameter for arterial stiffness which is a marker of cardio-vascular diseases. It was reported that a CAVI of ≥8 was a vital cut-off value associated with the presence of coronary artery disease with a sensitivity of 92.0%, a specificity of 73.0%, and an accuracy of 79.0%.[8] CAVI is essentially independent of blood pressure at the time of measurement, which makes it superior to brachial-ankle pulse wave velocity (baPWV), a conventional parameter that has been widely used in clinical practice previously.[9]

There have been several previous studies on smoking and PAD. However, these studies have investigated PAD in relation to many confounding diseases related to PAD such as diabetes, hypertension, and hyperlipidemia. In our study, we wanted to specifically examine the relationship between PAD and smoking without any confounding factors by recruiting smokers and non-smokers who had no underlying diseases which may have impacted our results.

The purposes of our research were to study differences of ABI and CAVI values between smokers and non-smokers and determine if there was an association between cigarette smoking and peripheral arterial conditions in terms of arterial occlusion and stiffness as reflected by ABI and CAVI, respectively. This research hypothesized that there are differences in ABI and CAVI values between smokers and non-smokers. Positive relationships between ABI and CAVI values and smoking behaviours were also expected.

Research methodology

This research was a cross-sectional analytical study. Ethical approval for this research was given by the Naresuan University Institutional Review Board (No. 52 01 01 0008). This study was performed in agreement with the principles of the Declaration of Helsinki. All participants provided a signed written consent form before being accepted into the study.

The participants

The participant population was recruited from Thapho district, Phitsanulok province, Thailand. A purposive sampling of 141 adults (aged ≥18 years old) without underlying diseases was performed. The participants consisted of 49 smokers and 92 non-smokers. The sample size was calculated as in the following equation:

$$n = \frac{\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2 2\sigma^2}{\left(\mu_0 - \mu_1\right)^2}$$

α is set at 0.05 that is equal to the $Z_{\alpha/2}$ value of 1.96

β is set at the power of 85% that is equal to the Z_{β} value of 1.037

μ_0 is the population mean for the control group (μ_0= 7.23)

μ_1 is the population mean for the experimental group (μ_1=7.94)

σ^2 is variance of population value (σ^2=1.77)

While the required sample size (n) for this study was nominally 128 participants, according to the calculation from a previous study[10], we included an extra number of

participants to avoid incomplete data, and to compensate for any participants withdrawing during the period of the study.

Non-smokers and smokers who had been smoking cigarettes for at least ten years were included. Any potential participant with an underlying disease, including peripheral artery diseases, diabetes mellitus and hypertension, were excluded from the study, as well as those who had been taking any medicine or dietary supplements in the three months prior to the commencement of the study.

Material and Method

Following the recruitment of the participants, blood pressure measurements were taken twice using a sphygmomanometer (Omron, Japan) to ensure a correct blood pressure reading for the participant. The participant's weight and height were measured using standard methods in order to calculate body mass index (BMI), and all were further assessed for vascular health, particularly arterial occlusion and arterial stiffness according to the ABI or CAVI. The medical histories of the participants were recorded, together with other lifestyle information, such as exercise regime together with demographic information, medical history, and smoking behaviours. The extent and validity of the questionnaire used had been approved by 3 health professionals. An index of item-objective congruence result of greater than 0.5 demonstrated the validity of the questionnaire. The participants were organised into groups according to their cigarette consumption and smoking duration, as indicated in their responses to the questionnaire. Cigarette consumption was categorised into 4 groups, based on the number of cigarettes smoked per day: 0 (never smoked), 1-5, 6-10, and ≥11. Smoking duration was again categorized into 4 groups according to the length of time the participant had smoked cigarettes; 0 year (never smoked), regularly smoked for 10-15 years, 16-20 years, and more than 20 years. All measurements were performed at the Department of Cardio-thoracic Technology, Faculty of Allied Health Sciences at Naresuan University, Thailand.

ABI and CAVI measurements

In order to measure ABI and CAVI values, a vascular screening device (VS-1500 N, Fukuda Denshi, Japan) was used. Before the measurements, the participants were asked to lie down and rest for five minutes. The procedures were done by trained technicians following the manufacturer's instructions. Blood pressure cuffs were placed on both arms and legs of the subjects. Electrocardiograms and phonocardiograms were also taken. All four blood pressure cuffs were inflated simultaneously, and the blood pressure readings and ABI and CAVI values were then recorded by a machine printout. The measurements were performed twice to obtain the average values of the parameters. The ABI abnormal values were defined as ≤0.90 for arterial occlusion[11], while the CAVI interpretation used a cut-off value ≥9 for suspected arterial stiffness.[12]

Statistical analysis

Data were recorded as mean±standard deviation (S.D.). All analyses were performed using Statistical Package for the Social Science (SPSS) for Windows version 17.0 (SPSS Inc., Chicago, IL, United States). The Kolmogorov Smirnov test was done for checking normal distribution of data. Comparisons between the smoker and non-smoker groups were performed using an independent samples t-test for continuous outcomes and chi-square (χ^2) test for categorical outcomes. The one-way ANOVA test was used for comparing continuous data from more than two groups after the groups were divided into subgroups. Statistically significant differences between groups were assessed using the p-value from the Tukey's post-hoc test. Simple regression analysis and stepwise multiple

regression analysis were performed to evaluate associations between CAVI and clinical parameters. Correlation between the two parameters (CAVI and smoking, and ABI and smoking) were assessed using the Pearson product-moment correlation coefficient. The p-value<0.050 was considered statistically significant in all tests.

Results

Demographic characteristics of subjects

One hundred and forty one participants were divided into two groups; non-smokers (92 participants, 65.2%) and smokers (49 participants, 34.8%), as shown in Table 1. The mean ages of the non-smokers (38.4±11.8 years old) and the smokers (41.4±10.7 years old) was not significantly different. The percentage of males was significantly differed (37.0% of non-smokers, 83.7% of smokers) while the mean of body mass index (BMI) between the non-smokers (23.59±3.60 kg/m^2) and the smokers (23.33±3.79 kg/m^2) was not significantly different.

Table 1 Demographic characteristics of participants

	Subject group		P-value
	Non-smoker (n=92)	Smoker (n=49)	
Age (years)	38.4±11.8	41.4±10.7	0.141
Male (n (%))	34 (37.0)	41 (83.7)	<0.001*
BMI (kg/m^2)	23.59±3.60	23.33±3.79	0.693

Notes: values are displayed as mean±standard deviation and n (%)
*represents statistical significance
BMI=body mass index

The CAVI values in the smokers differed from the non-smokers

Table 2 shows that the mean ABI of the smokers (1.09±0.09) did not differ significantly from that of the non-smokers (1.10±0.07) at p-value=0.642. As well, the ABI values from the right and left sides of the participants, which were separately analysed, were not different among the two groups. In contrast, the mean CAVI values of the smokers (7.88±1.26) and the non-smokers (7.17±0.94) were significantly different at p-value<0.001. Similarly, the right and left sides CAVI values of the participants were significantly different between the two groups at p-value< 0.001 and p-value=0.002, respectively. According to the CAVI interpretation, a cut-off value of ≥9 indicates suspected arterial stiffness. The results showed that the percentage of the smokers who had CAVI ≥9 (16.3%) was significantly different to that of the non-smokers (4.4%) at p-value=0.015.

Table 2 Ankle-brachial index and cardio-ankle vascular index values of participants

	Subject group		P-value
	Non-smoker (n=92)	Smoker (n=49)	
ABI			
Right	1.09±0.08	1.08±0.11	0.379
Left	1.10±0.08	1.10±0.09	0.903
Mean	1.10±0.07	1.09±0.09	0.642
CAVI			
Right	7.17±0.93	7.95±1.27	<0.001*
Left	7.18±0.98	7.80±1.32	0.002*
Mean	7.17±0.94	7.88±1.26	<0.001*
The cut-off of mean CAVI			
at ≥9.00 (n (%))	4/92 (4.4)	8/49 (16.3)	0.015*
at <9.00 (n (%))	88/92 (95.7)	41/49 (83.7)	

Notes: values are displayed as mean±standard deviation
*represents statistical significance
ABI=ankle-brachial index, CAVI=cardio ankle vascular index

Age and smoking were independent parameters associated with CAVI

The association between CAVI and clinical parameters was evaluated (Table 3). From univariate analysis, the CAVI value was associated with age (β=0.065, p-value<0.001), gender (β=-0.343, p-value= 0.029), BMI (β=-0.042, p-value=0.026), and smoking (β=0.340, p-value=0.037). For further investigation, stepwise multiple regression analysis was performed. We found that age (β= 0.064, p-value<0.001) and smoking (β=0.349, p-value= 0.036) were independent parameters associated with CAVI.

The number of cigarettes smoked per day was positively related to CAVI

The smokers were categorised into 3 groups, based on the number of cigarettes smoked per day: 1-5, 6-10, and >11. The non-smokers comprised a 4th group for this purpose. We first compared the difference of CAVI among the 4 groups. The mean CAVI values were significantly different among the four groups analysed by ANOVA (p-value=0.003). With further analysis by Tukey's post-hoc test, we found that the mean CAVI of the smokers in the >11 cigarettes a day group (8.17±1.14) was significantly different than that of the non-smokers (7.17±0.94) at p-value=0.040 as shown in Figure 1a. Further assessing the relationship between the number of cigarettes consumed per day and the mean CAVI analysis found that the amount of tobacco consumption was statistically related to increased mean CAVI values (r=0.31, p-value<0.001) as shown in Figure 1b. Smoking duration was positively related to CAVI The smokers were categorized into 4 groups according to the length of time they had smoked cigarettes: never smoked (0 year), regularly smoked for 10-15 years, 16-20 years, and more than 20 years. We found that there were significant differences of the mean CAVI among the four groups (p-value<0.001). In particular, the mean CAVIs of the 'more than 20 years' group (9.19±1.85) were significantly different to that of non-smokers (0 year) (7.17±0.94) (p-value<0.001) and the regularly smoked for 10-15 years (7.52±0.86) (p-value<0.001) and 16-20 years (7.89±1.12) (p-value=0.031) groups (Figure 2a). When correlation evaluation was performed, the results showed that smoking duration was statistically related to increased CAVI values (r=0.42, p-value<0.001) (Figure 2b).

Table 3 The associations between CAVI, demographic characteristics, and smoking

Parameters	Univariate analysis				Multivariate analysis			
	Beta	95% CI		P-value	Beta	95% CI		P-value
		Lower	Upper			Lower	Upper	
Age (years)	0.065	0.053	0.077	<0.001	0.064	0.052	0.076	<0.001
Gender	-0.343	-0.651	-0.036	0.029	–	–	–	–
BMI (kg/m^2)	-0.042	-0.078	-0.005	0.026	–	–	–	–
Smoking	0.340	0.020	0.660	0.037	0.349	0.023	0.674	0.036

CAVI=cardio ankle vascular index, CI=confidence interval, BMI=body mass index

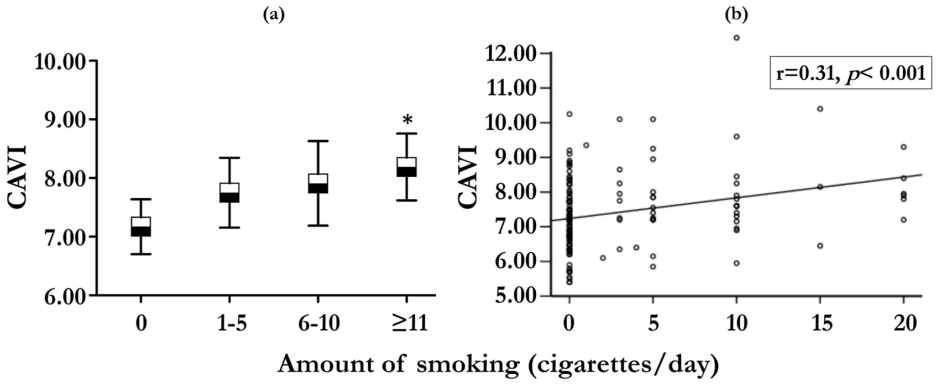

Figure 1 (a) The differences in CAVI values according to the amount of smoking (* represents significant differences of CAVI values between the highest cigarette-consuming group, ≥11 cigarettes per day, and the non-smoking group at p-value=0.040). (b) Showing the calculation of the Pearson product-moment correlation coefficient between CAVI values and amount of smoking.

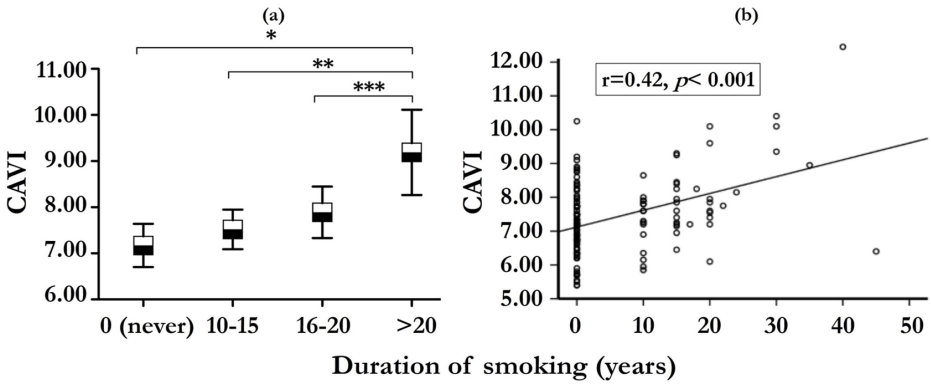

Figure 2 (a) The differences in CAVI values according to duration of smoking [*(p-value<0.001), **(p-value<0.001), and ***(p-value=0.031) represent the significant differences of CAVI values among the 4 groups: as never smoking (0 year), regularly smoking for 10-15 years, 16-20 years, and more than 20 years]. (b) Showing the calculation of the Pearson product-moment correlation coefficient between CAVI values and duration of smoking.

Discussion

In this study, we evaluated peripheral vascular conditions among smokers in terms of arterial stiffness and occlusion. Two measures were used in the study: the CAVI, which is a new screening indicator of arterial stiffness, and the ABI, which is a parameter representing arterial occlusion. The results showed that the average CAVI value of smokers was significantly higher than

that of non-smokers. Age and smoking were the only significant factors influencing the CAVI. Moreover, a greater number of cigarettes smoked per day and longer smoking duration were significantly positively correlated to the CAVI values. However, no difference in the ABI readings was found between smokers and non-smokers.

Previous studies have shown that tobacco smoking causes vascular diseases, in particular arteriosclerosis[13,14], and that there is a relationship between smoking and PAD.[15,16] However, only a small number of studies have assessed the association of smoking and arterial stiffness in adults without underlying diseases. Our analysis focused on the length of time that the participants had been smokers, and their average number of cigarettes smoked per day.

Theoretically, the CAVI scores reflect arterial stiffness. Soft and flexible arteries give a low CAVI score, while arteriosclerotic arteries, which are less flexible, result in a high CAVI value. Generally, an increase in arterial stiffness is related to an increase in BMI and age, especially in persons 60 years or older.[17,18] One of the strengths of our study was that potentially confounding variables such as BMI and age were well matched between the smokers and the non-smokers. In this study, the average BMI of the participants was in the normal range. From our multivariate analysis of the CAVI and risk factors, age and smoking were determined as the two significant factors influencing CAVI. However, both the average and median ages of the participants were about 40 years old, thus arterial stiffness related to age can reasonably be excluded, meaning that the CAVI results in our study more correctly reflect arterial stiffness related to smoking. In our study, the CAVI value of smokers (7.88±1.26) was significantly different than that of non-smokers (7.17±0.94). According to the recommendations of the manufacturers of the CAVI equipment, a CAVI <8.0 is normal, while the ≥8 and <9 CAVI is considered as borderline. A CAVI ≥9 leads to the diagnosis of suspected arteriosclerosis.[12] Not all studies have supported this recommendation, for example a report on the average CAVI in a high-risk for cardiovascular disease (CVD) group found the average CAVI of <9.[19] This study reported average CAVI scores in the CVD risk-free group and the CVD high-risk group. For the CVD risk-free group at 40-49 years of age, the average CAVI score of males was 7.59±0.70 and that of females 7.29±0.66. For the CVD high-risk group at the same age range, the average CAVI score of males was 7.79±0.85 and that of females 7.58±0.91.[19] Moreover, a CAVI of ≥8 was reported as the best cut-off value associated with the presence of coronary artery disease.[8] Thus, the CAVI score of the smokers in this study, which was higher than that of the non-smokers, indicates the higher risk of cardiovascular disease. In addition, the percentage of the smokers with CAVI ≥9 was significantly higher than that of the non-smokers. Accepting this cut-off value would indicate that the percentage of smokers with probably arterial stiffness was significantly higher than that of the non-smokers.

Furthermore, we found that the increase in CAVI had a positive relationship to both level and duration of tobacco consumption. This finding was consistent with previous reports[20-22] which found that the acute baPWV of chronic smokers was significantly higher than that of non-smokers. The increased baPWV of longterm smokers vs non-smokers was also significantly extended in long-term measurement.[23] According to ABI, no differences in ABI values were found between smokers and non-smokers in the present study. This might be explained by the ABI having a high specificity (86.0%) with moderate sensitivity (75.0%) for arterial occlusion.[7] It was reported that ABI ≤0.9 is an effective parameter for serious arterial occlusion (≥50% stenosis).[7] In fact, however, arterial

occlusion develops slowly over ten or more years until clinical manifestation.[24] Thus, the presence of an abnormal ABI from arterial occlusion may take a longer time than an abnormal CAVI.[25-27] An abnormal CAVI is therefore an early parameter of arterial stiffness as a result of arteriosclerosis. We suggested that CAVI is a beneficial index, as a screening tool of overall arterial stiffness caused by smoking.

There are many poisonous chemicals in cigarette smoke which can contribute to arterial stiffness such as nicotine, free radicals, and aromatic compounds which impair vascular endothelial cells.[28,29] Endothelial dysfunction causes several problems leading to atherosclerosis.[30,31] However, further investigations are needed to elucidate the pathophysiological mechanisms that link smoking and arterial stiffness.

The one notable limitation of the present study was the small sample size, which could have affected subgroup analysis and outcomes, especially in female smokers. For higher quality research, we suggest further studies with larger sample sizes, especially in the number of female smokers, and conducting using a prospective cohort study.

Conclusion

The present study demonstrated that the CAVI of smokers without underlying diseases who had been consuming cigarettes for more than 20 years was significantly different to those of smokers with lower smoking durations and non-smokers. The study, however, found no differences in ABI values between smokers and non-smokers. Age and smoking duration and quantity were the significant influential factors related to the CAVI scores.

Acknowledgement

This research was supported by grants from Faculty of Allied Health Sciences Research Funding, Naresuan University, Thailand. Many thanks to Mr.Roy Morien of the Naresuan University Language Centre for his editing assistance and advice on English expression in this document.

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