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ช่วงเวลาเคลื่อนผ่านของชีพจรในผู้สูงอายุดังตัวชี้วัดทางชีวภาพของความเสี่ยงต่อภาวะสมองเสื่อม

Pulse transit time in ageing as early biomarker for risk of dementia

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บทคัดย่อ: *งานวิจัยนี้ ศึกษาความแตกต่างระหว่างกลุ่มผู้สูงอายุที่ไม่มีภาวะ และมีภาวะสมองเสื่อม (Dementia) โดยการเปรียบเทียบค่าช่วงเวลาเคลื่อนผ่านของชีพจร (Pulse transit time) ที่แสดงถึงสภาวะความแข็งของหลอดเลือดแดง และความดันโลหิต จากการเก็บข้อมูลค่าช่วงเวลาเคลื่อนผ่านของชีพจรในท่านอนหงาย ผลคะแนนจากแบบทดสอบภาวะสมองเสื่อม (MMSE) ค่าความดันโลหิต และอัตราการเต้นของหัวใจ ในอาสาสมัครจำนวน 28 ราย พบว่า ค่าช่วงเวลาเคลื่อนผ่านของชีพจรมีความแตกต่างกันระหว่างกลุ่มอย่างมีนัยสำคัญทางสถิติ (P = 0.039) ผลการศึกษานี้ แตกต่างจากหลายการศึกษาที่ผ่านมา เนื่องจากพบค่าช่วงเวลาเคลื่อนผ่านของชีพจรในกลุ่มที่ไม่มีภาวะสมองเสื่อมสั้นกว่ากลุ่มที่มีภาวะ ด้วยเหตุนี้ จึงอภิปรายผลในแนวทางปฏิทรรศน์ของหัวใจและหลอดเลือด (Cardiovascular paradox) สำหรับผู้สูงอายุ กล่าวคือ ค่าช่วงเวลาเคลื่อนผ่านของชีพจรที่สั้นกว่านั้น เป็นผลมาจากสภาวะความแข็งของหลอดเลือดแดงร่วมกับค่าความดันโลหิตที่สูง ส่งผลให้อัตราการไหลเวียนเลือดในสมองเพิ่มขึ้น ซึ่งสัมพันธ์กับการลดความเสี่ยงจากภาวะสมองเสื่อม งานวิจัยนี้นำเสนอการตรวจสอบภาวะสมองเสื่อมด้วยวิธีการวัดค่าช่วงเวลาเคลื่อนผ่านของชีพจร สู่แนวทางในการพัฒนาวิธีตรวจสอบอาการขั้นต้น หรือก่อนแสดงภาวะสมองเสื่อม เพื่อประโยชน์ในการป้องกันภาวะสมองเสื่อมสำหรับผู้สูงอายุ*

ABSTRACT: *A pulse transit time (PTT) was performed as an indicator of arterial stiffness and blood pressure. This aimed to examine a difference between with and without dementia groups in an ageing people. Twenty-eight participants were given their PTT values in a supine posture. The Mini-Mental State Examination scores, systolic blood pressures, diastolic blood pressures, and heart rates were collected in each individual. The main finding was showed that the PTT differed between the groups (P = 0.039). Interestingly, the non-dementia group produced a shorter time of the PTT than the dementia group. This was unaligned evidence to numerous studies. It raised an ageing aspect of a cardiovascular paradox into an explanation. The present study supported that the short time of the PTT was affected by an interaction between the arterial stiffness and the high blood pressure. It was increased a cerebral blood flow, which was lowered to the risk of dementia. The present study summarized that the PTT parameter was an appropriate non-invasive measurement for detecting the development of dementia. In the ageing people, detecting dementia at a pre-stage was beneficial and recommended.*

คำสำคัญ: *ช่วงเวลาเคลื่อนผ่านของชีพจร ผู้สูงอายุ ภาวะสมองเสื่อม*
Keywords: *Pulse transit time, Ageing, Dementia.*

1. INTRODUCTION

The pulse transit time (PTT) is a clinical non-invasive measurement for cardiovascular studies. An interval time difference between a peak of an R wave from electrocardiography (ECG) and a peak of pulse wave from a predetermined peripheral site, usually at a finger, toe, or an earlobe, is the PTT [1]. Generally, arteries transport blood circulation from the heart through the entire body. A contraction of the heart generates an energy pulse wave, where is running through the circulatory system. A travel speed of the pulse wave is associated with mechanical properties, elastance and compliance, of the arteries. Not only to expand, but abilities of the arteries are also to recoil. There are depending on levels of pressure. The duration of the pulse pressure wave, between the two arterial sites, that travels through the arterial tree is well known as the PTT.

The speed at which the arterial pressure wave travels is directly affected to a proportion of the blood pressure. An increase in blood pressure causes an excessive vascular tone. Then the arterial wall becomes stiffer leading to a shortening of the PTT. In contrast, a falling of the blood pressure causes a decreasing of the vascular tone. It affects an enlarging of the PTT [2]. Ageing people leads to an increase in the arterial stiffness and blood pressure, which decreases in the PTT. Thus, the PTT value depends on the levels of the arterial stiffness and the blood pressure [3].

Previous studies indicated that the PTT was an assessment for the arterial stiffness [4] and the blood pressure [5]. The arterial stiffness was linked to high blood pressure as a cause and a consequence [6]. A meta-analysis study indicated that a higher level of the arterial stiffness was associated with markers of cerebral small-vessel disease [7]. This was increased faster cognitive decline and risk of dementia [8]. Besides, a systematic study indicated that high blood pressure, hypertension, was associated with risk factors for vascular diseases as well as a neurological disorder [9]. This was an increased risk of developing cognitive impairment and dementia in the ageing people [10].

In terms of a global cognitive impairment test, the Mini-Mental State Examination (MMSE) was used widely to screen for dementia in the ageing people [11]. A 12-year ageing study in Japan was characterized participants with their average scores of the MMSE into groups of a high score (28.8 points), a middle score (25.7 points), and a low score (19.9 points). It resulted that the middle and low score groups had a higher risk of incident disabling dementia compared to the high score group [12]. A previous study of dementia in Parkinson's disease was validated the MMSE for detection in the ageing people. It resulted that an optimal screening cutoff score was 28 or 29 points with a sensitivity of 0.82 and a specificity of 0.63 [13]. A past study of cognitive impairment was carried out in participants between 55 and 85 years without previously known cognitive deficits. It resulted that the MMSE score of 28 or lower, a sensitivity of 0.85 and a specificity of 0.66, was showed cognitive dysfunctions [14]. Also, a study of mild cognitive impairment indicated that an overall standardized MMSE cutoff score of 28 was for cognitive impairment including dementia [15]. It could be seen that the MMSE score of 28 points was a reasonable cutoff for detecting dementia in the ageing people.

However, there was an unclear that whether the PTT could be an indicator for detecting dementia. Therefore, the present study aimed to investigate a difference of the PTT between with and without dementia groups in the ageing people.

2. METHODS

2.1 Participants

The present study was recruited 28 Thai participants, which was 8 males and 20 females. They were aged between 63 and 87 years. The participants who unable to complete the MMSE and having records of heart diseases or cardiovascular diseases, e.g. congestive heart failure, abnormal heart rhythm, stroke, and arrhythmia were excluded. All were classified as a non-dementia group and a dementia group based on the results of the MMSE. As mentioned earlier, the cutoff score of 28 points, 27 points or below, for detecting dementia was used in the present study. Fourteen participants, therefore, were characterized by each group. The present study was approved by the Institutional Review Board of Faculty of Medicine, Thammasat University (MTU-EC-DS-6-069/59), and written informed consent was obtained from each participant.

2.2 MMSE Measurement

The MMSE in Thai version, MMSE-Thai 2002, was used to perform in the present study. The MMSE consisted of 30 subitems. In all the items, each correct answer scored 1 point and each incorrect answer scored 0. The maximum score that could be obtained was 30 and the minimum was 0 [16]. The MMSE was measured by trained research staffs. It took approximately 10-15 minutes of each participant. The measurement was followed by guidelines for administration of the standardized MMSE [17].

2.3 Blood Pressure and Heart Rate Measurements

After 5-minute rest in a seated position, the measurements of the blood pressure and the heart rate were taken on the right upper arms. During the measurements, the participants were asked to sit in the chair with their feet on the floor. Elbows were supported at about levels of their hearts. The measurements were assessed by an automatic arm blood pressure monitor. The results of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were collected.

2.4 PTT Measurement

The participants were asked to refrain from ingesting caffeine in at least 12 hours before the measurement. They were asked to wear comfortable shirts and shorts, where were non-conductors of electricity. All were asked to take off all accessories, e.g. glasses, watches, rings, earrings, necklaces, bracelets, keys, wallets, or any wearable metals. The ECG, bipolar limb leads, was performed with a sampling rate of 1,000 Hz. A two-lead method [18] was recorded electrical difference between the right wrist (negative) and left ankle (positive) electrodes. The participants were asked to wear the PTT devices at all times during the measurement. There were electrodes for a right wrist and both ankles with a single pulse clip for the tip of the index finger. The measurement was assessed by the PowerLab 26T model and recorded with the LabChart software (AD Instruments). All were supported by the Faculty of Medicine, Thammasat University.

To perform the measurement, the participants were asked to lie on their backs horizontally. Arms were relaxed at the side of their bodies. Faces, torsos, forearms and palms were faced up. Feet were relaxed and aligned with their shoulders. The measurement was recorded for 10 minutes of each participant as shown in Figure 1.

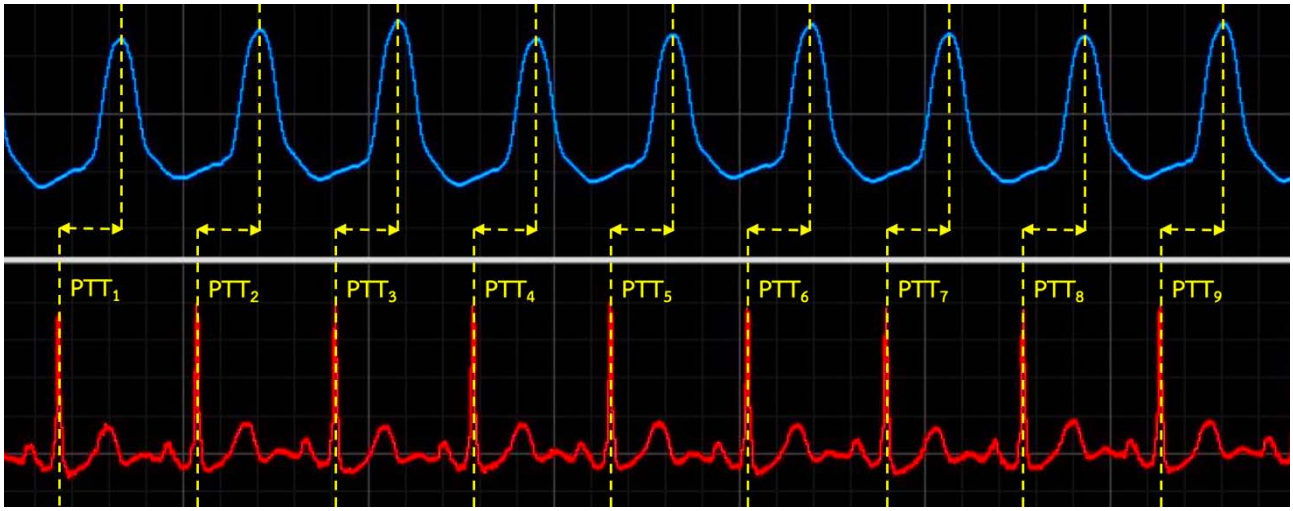

Figure 1: **Samples of PTT calculation**

Continuous lines in blue and red colours were displayed the pulse and ECG signals respectively. All dash lines in a yellow colour were displayed the PTT calculation. Vertical dash lines were indicated the peaks of the R waves (in a lower row) from the ECG and the peaks of the pulse (in an upper row). Horizontal dash lines were indicated the interval time between the peaks, which were collected for the results of the PTT.

2.5 Statistical Analysis

Descriptive statistics of the participants were described in means (M) and standard deviations (±SD). Differences in the means between the groups were presented in mean differences (MD). A nonparametric test of homogeneity of variance was performed with the Levene's test (*F*), which was based on median and with adjusted degrees of freedom. Medians, ranges, and interquartile ranges (IQR) were informed for the PTT as well as mean ranks. A difference of the PTT between the groups was compared with the Mann-Whitney U test, which was presented with a Z score (*Z*) at a significance level of 0.05 (two-tailed). The effect size for the nonparametric test [19] was calculated with the Eta-squared (η^2).

3. RESULTS

The non-dementia group had 2 males and 12 females, which was aged M = 75.43, SD = ±6.94 years. The group gained the MMSE score of M = 29.21, SD = ±0.80 points. The SBP was M = 148.93, SD = ±20.93 mm Hg. The DBP was M = 71.64, SD = ±10.51 mm Hg. The heart rate was M = 78.00, SD = ±9.50 beats per minute. They spent M = 0.22, SD = ±0.02 seconds for the PTT. In addition, the dementia group had 6 males and 8 females, which was aged M = 74.57, SD = ±6.77 years. The group gained the MMSE score of M = 23.64, SD = ±2.87 points. The SBP was M = 144.29, SD = ±13.99 mm Hg. The DBP was M = 70.64, SD = ±11.76 mm Hg. The heart rate was M = 78.43, SD = ±6.27 beats per minute. They spent M = 0.23, SD = ±0.02 seconds for the PTT as shown in Table 1.

Table 1: **Descriptive statistics of participants**

	Non-dementia (n = 14)	Dementia (n = 14)
Gender (males/females)	2/12	6/8
Age (years)	75.43 (±6.94)	74.57 (±6.77)
MMSE (points)	29.21 (±0.80)	23.64 (±2.87)
SBP (mm Hg)	148.93 (±20.93)	144.29 (±13.99)
DBP (mm Hg)	71.64 (±10.51)	70.64 (±11.76)
Heart rate (beats per minute)	78.00 (±9.50)	78.43 (±6.27)
PTT (seconds)	0.22 (±0.02)	0.23 (±0.02)

The non-dementia group was aged than the dementia group (MD = 0.86). The mean of the MMSE in the non-dementia group was higher than the dementia group (MD = 5.57). Both the systolic and diastolic blood pressures in the non-dementia group were elevated than the dementia group (MD = 4.64 and MD = 1.00 respectively). The overall of the heart rate in the non-dementia group was slower than the dementia group (MD = -0.43). The average of the PTT in the non-dementia group was shorter than the dementia group (MD = -0.02).

Histograms, box plots, and normal Q-Q plots were visually inspected for both groups. None were normally distributed. Their distributions were not sufficiently normal for purposes of conducting the Independent *t*-test. Therefore, the Mann-Whitney U test was performed in the present study. No statistically significant differences were found between the groups, except for the PTT. Then, an assumption of homogeneity of variance was tested and satisfied with the nonparametric Levene's test, F (1, 23.58) = 0.11, P = 0.743.

Table 2: **PTT between groups**

	Non-dementia (n = 14)			Dementia (n = 14)			P value
	Median	Range	IQR	Median	Range	IQR	
PTT (seconds)	0.22	0.06	0.03	0.23	0.07	0.03	0.039*

*Significant at P < 0.05

The non-dementia group was associated with the PTT median = 0.22 (range = 0.06, IQR = 0.03). By comparing, the dementia group was associated with a numerically larger the PTT median = 0.23 (range = 0.07, IQR = 0.03) as shown in Table 2. Additionally, the non-dementia group was associated with a mean rank of 11.29 and the dementia group was associated with a mean rank of 17.71. At least numerically, the non-dementia group, on average, timed smaller than the dementia group. There was a statistically significant difference in the PTT between the groups, Z = -2.068, P = 0.039. The nonparametric η^2 was estimated at 0.15, which was a relatively small to typical effect based on Gignac and Szodorai's guidelines [20].

4. DISCUSSION

The results showed that the dementia group gained more time in the PTT than the non-dementia group in the mean and median values. Unexpectedly, the short PTT was found in the non-dementia group, which was implied to the high levels of the arterial stiffness and the blood pressure. These pieces of evidence were inconsistent with several past studies [21-23]. Interestingly, an explanation was recently made in a systematic review in the aspect of the cardiovascular paradox for the ageing people. It indicated that the high blood pressure, systolic or diastolic, in a young adult people was associated with cognitive impairment. In contrast, the high arterial blood pressure in the ageing people was considered as a protective factor for cognitive functioning [24]. These were aligned with the results of the present study.

Several studies indicated that low blood pressure was related to the risk of dementia [25-28]. Since the decreased of the blood pressure affected in the reducing of the velocity of the cerebral blood flow. This damage caused to neural tissues and could be extended to the pathological mechanisms of cognitive dysfunction [29]. Lowered in the cerebral blood flow has been found in the ageing with dementia as well as in those presenting early symptoms of dementia [30]. In the advanced age, previous studies, participants aged 75 years and above, indicated that the lower arterial blood pressure was correlated with the poor performance of the cognition [31, 32]. Also, a study on participants aged 90 years and centenarian indicated that the high blood pressure as the hypertension was not directly related to the decline of cognitive functions [33]. This illustrated that the low blood pressure potentially played an important role in the risk of dementia. It could be seen that, with increasing age, the higher arterial stiffness combined with the low blood pressure would be a critical concern. This could be even more significantly worse in a situation of an old-old population or a frail ageing people.

Additionally, a U-shaped association between blood pressure and cognitive impairment or dementia was suggested by an ageing population study in China. It indicated that both higher and lower levels of the blood pressure of systolic, diastolic, and the mean arterial pressures were associated with a higher risk of cognitive impairment [34]. Some studies indicated that both high and low blood pressures may be related to cognitive dysfunction [35, 36]. These pieces of evidence illustrated that a relationship between the blood pressure and the cognition was detailed. There was a complex interacted between the two variables, which was unlikely linked to a linear correlation.

Strengths were mentioned in the present study. All the assessments were the non-invasive measurements. All the experiments were conducted with a high level of the safety standard for the ageing people. None of the participants was reported health-related issues from the measurements. Limitations were that the participants had a low number of the sample size with an unbalanced gender. There was no confirmation from medical doctors, neurologists, psychologists, psychiatrists, or related specialists in a diagnosis for the dementia group. Also, there were no dementia patients participated in the present study. Thus, it would be suggested to use the PTT as an additional tool with specialists rather than as a standalone index in identifying dementia in clinical trials. Even the result was showed the statistically significant but the strong evidence remained unclear. More studies of the PTT in clinical investigations as substantial materials are needed. Future studies are required to clarify the interplay between the arterial blood pressure and dementia in the ageing people. It would be useful to investigate further aspects that whether the PTT could potentially be an index or an indicator for the age-related cardiovascular diseases such as a coronary artery disease or a frailty syndrome.

5. CONCLUSION

The PTT could differentiate between the with and without dementia groups in the ageing people. The use of the PTT was contributed as the estimator for the levels of the arterial stiffness and the blood pressure within the same range of age. The present study was concluded and insisted with the notion of the cardiovascular paradox for the ageing people. The greater of the arterial stiffness was related to age increased. However, the higher of the blood pressure, the shortening of the PTT, was associated with the low risk of dementia. Conversely, the lower of the blood pressure, the lengthening of the PTT, was drawn to dementia. The PTT was played an important role in identifying dementia in the present study. This was extended the further evidence to the benefit of the PTT, which was complemented to a preventive strategy tool against early-onset dementia. It should be noted that the PTT in the study was a piece of preliminary evidence. Using the PTT as an isolated clinical tool with non-specialists would unrecommended. Lastly, the present study prompted to healthcare providers to carefully more before treatments were made, generally to lowering the blood pressures, for the ageing people.

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