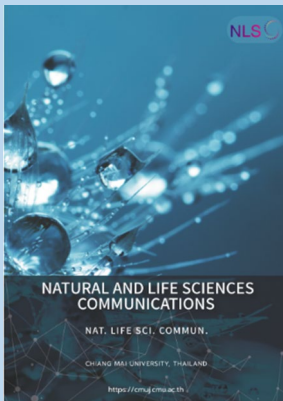


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Effects of Occlusion Cuff Pressures for Determining Brachial Artery Flow-Mediated Dilation in Healthy Thai Adults

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ABSTRACT

Variability in cuff occlusion pressure used during flow-mediated dilation (FMD) measurement may cause differences in FMD results and discomfort sensation. The objective of this study was to compare FMD data and sensations of pain and numbness using three levels of occlusion cuff pressures commonly used for FMD assessment in healthy adults. A within-subject design was conducted in 12 healthy adults aged 20-40 years. FMD was measured using brachial artery Doppler ultrasound at three different occlusion pressures: 25 and 50 mmHg above systolic blood pressure (SBP) and 200 mmHg. Pain and numbness were recorded using the Numeric Pain Rating Scale and the Visual Analog Scale, respectively, at baseline and every minute during the 5-minute occlusion and 3 minutes after cuff deflation. The results showed that %FMD and mean blood flow velocity after using cuff pressure at 25 mmHg above SBP ($10.11 \pm 2.58\%$ and 11.52 ± 3.96 cm/s) were comparable to those of 50 mmHg above SBP ($10.08 \pm 2.70\%$ and 12.54 ± 4.31 cm/s) and at 200 mmHg ($10.15 \pm 2.74\%$ and 12.28 ± 4.30 cm/s) (all $P > 0.05$). The pain intensity was significantly greater at 200 mmHg compared to 25 mmHg at the first, second, and fourth minutes during occlusion (all $P < 0.05$). The numbness scale was not different among the three pressure conditions. In conclusion, the minimum occlusion pressure above SBP by 25 mmHg generated an insignificant FMD response compared to the other two cuff pressures, caused minor pain, and may be the favorable pressure for determining endothelium-dependent FMD in healthy Thai adults.

Keywords: Flow-mediated dilation, Occlusion cuff pressure, Pain sensation, Adults



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INTRODUCTION

Flow-mediated dilation (FMD), a surrogate marker of endothelium-dependent vasodilator function, is considered an important early event in preceding structural atherosclerotic changes (Moens et al., 2005; Thijssen et al., 2011). Studies have demonstrated a relationship between coronary endothelial function and the function of the brachial artery (Broxterman et al., 2019). Individuals with impaired brachial FMD had a significantly higher risk of cardiovascular events (CVs) than those with normal FMD (Heiss et al., 2022; Mućka et al., 2022). Moreover, the brachial FMD can independently predict long-term adverse CVs in healthy subjects (Shechter et al., 2014) and patients with cardiovascular disease (Inaba et al., 2010), which most of them may not be aware of their condition until an acute event (Sarrieff et al., 2014). Therefore, monitoring endothelial function as a preventive measure for cardiovascular disease is important.

Endothelium-dependent FMD, which refers to the change in artery diameter in response to reactive hyperemia, can be measured using a standardized blood pressure occlusion (Bots et al., 2005). Elevations in blood flow-associated shear stress cause the vascular endothelium to release nitric oxide (NO), resulting in local arterial vasodilation. Thus, reduced NO bioavailability may play a role in the pathogenesis of vascular disease (Bots et al., 2005).

Factors known to affect FMD results include ultrasound settings, subject preparation, cuff size, occlusion site, and occlusion duration (Corretti et al., 2002; Harris et al., 2010; Thijssen et al., 2019). Additionally, the pressure of the occlusion cuff is crucial for FMD measurements, as it impacts the shear stress stimulus and the NO-dependent dilation response (Thijssen et al., 2019). Previous literature has reported variability in the occlusion cuff pressures used, with common ranges being 25–50 mmHg above systolic blood pressure (SBP) and between 200–300 mmHg (Thijssen et al., 2019). A meta-analysis revealed no significant difference in the mean value of FMD responses between occlusion pressures above or below 275 mmHg (Bots et al., 2005). Expert consensus guidelines recommend using cuff pressure exceeding 50 mmHg above SBP to prevent arterial inflow, noting that this pressure is well-tolerated and not associated with discomfort (Thijssen et al., 2019).

However, FMD results and the occurrence of discomfort sensations, including pain and numbness, in response to different cuff occlusion pressures during FMD assessments remains unclear. Additionally, it has been reported that pain perceptions can differ due to ethnic variations (Krupić et al., 2019; Rowell et al., 2011). Studies have shown that Asians tend to have lower sensory and pain thresholds but experience greater pain compared to both Caucasians and African Americans (Ramer et al., 1999; Rowell et al., 2011). Moreover, studies revealed that higher cuff occlusion pressure can increase discomfort, pain, and numbness during procedures as they compress nerves and blood vessels (Spitz et al., 2022). Appropriate use of cuff occlusion pressure may minimize these discomforts and the risks of injury associated with FMD measurement.

Therefore, this study aimed to compare FMD across three cuff occlusion pressures: 25 and 50 mmHg above SBP, and the typical occlusion at 200 mmHg. These pressures were selected based on previous research recommendations for inducing sufficient responses in FMD assessment. Specifically, 25 mmHg above SBP is the minimal recommended value, while 50 mmHg (moderate) and 200 mmHg (high) are commonly used pressures. Young healthy subjects were selected for this initial study to minimize the impact of confounding variables like age-related vascular changes (Seals et al., 2011), and comorbidities on FMD (Ray et al., 2023). Additionally, the scale of discomfort sensations, including pain and numbness, were compared among the three cuff pressures. We hypothesized that there would be no significant differences in FMD results between the three cuff occlusion pressures, while discomfort sensations would significantly differ between the pressures.

MATERIALS AND METHODS

Study design

Twelve healthy adults aged 20–40 years were voluntarily recruited via flyers placed at a university campus and around the community. All participants were recreationally active (≥ 600 metabolic equivalents (MET)-minutes per week) using the Global Physical Activity Questionnaire (GPAQ) (Cleland et al., 2014; Cortés et al., 2018). They were non-smokers and normotensive ($<128/80$ mmHg) (Whelton Paul et al., 2018). Participants did not have any known cardiac or medical conditions, diabetes, cardiovascular disease, peripheral artery disease, dyslipidemia, rheumatoid arthritis, and chronic kidney disease. None of the participants used any medications that interfered with the cardiovascular system (Thijssen et al., 2009). Participants who were unable to fully participate in the study were excluded. Before the commencement of the study, all participants signed informed consent documents approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (RAS; 0056), and the Thai Clinical Trials Registry (TCTR 20230822004).

Experimental design

A repeated-measures within-subject design was used. Eligible participants were randomly assigned to the order of occlusion cuff pressure for FMD assessment by a simple sampling method. Three levels of occlusion cuff pressure, at 25 and 50 mmHg above SBP and 200 mmHg, were examined with a 30-minute rest interval between each measurement. The outcome measures were FMD and levels of pain and numbness. FMD was determined at baseline and after the release period, while the levels of pain and numbness were recorded at baseline, during occlusion, and during release periods.

Brachial artery FMD assessments

The procedure of FMD assessment was conducted according to a previous study (Corretti et al., 2002; Sturm et al., 2009). Participants were asked to fast and refrain from a high-fat diet, caffeine, vitamin C, and exercise for at least 8–12 hours the night before the FMD assessment. Additionally, women were not to be in their menstrual period. FMD was assessed using a Doppler color ultrasound, pulsed wave Doppler mode (Xario 100, Toshiba, Japan) in a temperature-controlled room at 25°C with dim light. After 15 minutes of resting in a supine position, participants were instructed to abduct the arm at a 90° angle. An 11-MHz linear probe with the insonation angle at 60 degrees with sample volume to the vessel was scanned on the right brachial artery (Corretti et al., 2002; Sturm et al., 2009). This was conducted in a longitudinal section 4.5 cm above the antecubital fossa, ensuring the maximum lumen diameter (Wisløff et al., 2007). The scans were performed at the same time of day by a trained technician. The intra-rater reliability of the FMD measurement was within an acceptable range (ICCs = 0.90, $P < 0.001$). The standard error of measurement and the minimal detectable change were 0.92 and 2.54, respectively. The baseline of the brachial artery diameter (FMDbase) and mean blood flow velocity (MBFVbase) were measured using pulse wave Doppler at the well-rested stage. A sphygmomanometer cuff (Model HM-1101, Japan) was placed around the forearm and inflated for 5 minutes (Agewall et al., 2001; Corretti et al., 2002). After cuff release, the images were continuously recorded every 30 seconds for 2 minutes to measure the peak diameter of the brachial artery (FMDpeak) (Corretti et al., 2002; Rodriguez-Miguel et al., 2016). The absolute maximal diameter of the brachial artery at baseline (FMDbase) and after the release of cuff occlusion (FMDpeak) was calculated for %FMD by the formula $(\text{FMDpeak} - \text{FMDbase})/\text{FMDbase} \times 100$. In addition, mean blood flow velocity at baseline (MBFVbase) and after the release of cuff occlusion (MBFVpost-occlusion) were determined (Corretti et al., 2002).

Discomfort symptoms

Pain was assessed by a Numeric Pain Rating Scale (NPRS) from 0 (no pain) to 10 (worst imaginable) (Edwards, 2005; Katz and Melzack, 1999), while numbness was determined by a Visual Analog Scale (VAS) from 0 (none) to 10 (unbearable) (Hongwen et al., 2018). Both variables were recorded at baseline and every minute for 5 minutes during the 5-minute occlusion and were continuously recorded at 30-second intervals until the symptoms dissipated after cuff deflation. The 30-minute rest period between the three cuff pressures trials was designed to prevent habituation, ensuring that each pain assessment was not influenced by the previous stimulus (Rankin et al., 2009). Additionally, a 30-second interval was chosen for monitoring pain to capture significant changes, as studies have found that peak pain sensation typically occurs within 2 minutes (Estebe et al., 2000; Mitrichev et al., 2024).

Anthropometric data

Body weight (BW) was measured by weight scale (Omron HN289, Japan). Height was measured using a wall-mounted stadiometer (Health-O-Meter 402 KL, IL) to the nearest 0.1 cm, and body mass index (BMI) was subsequently calculated by using a formula: $BMI = BW \text{ (kg)} / \text{height}^2 \text{ (m)}$ (Senaratna et al., 2017).

Sample size calculation

There is no evidence studying the effects of occlusion pressure on FMD. Thus, the sample size of this study was estimated based on statistical principles (Maher et al., 2013) using G*Power 3.1.9.4 software. The sample size for FMD using two-way repeated analysis of ANOVA was computed with the effect size of 0.4, and the number of measurements was 3 with a power of 80% and a significance level of 0.05. Therefore, the total number of subjects was 12. The sample size for the pain scale using a two-way repeated measure ANOVA was calculated with an effect size of 0.4, with 12 repeated measurements, a power of 80%, and a significance level of 0.05. This calculation yielded a sample size of 6 individuals. Similarly, for the numbness measure, which was repeated 16 times, a sample size of 5 individuals was required. Consequently, the total number of participants in the study was 12 individuals.

Statistical analysis

All data was presented as mean $\pm$ SD. The normality and homogeneity of each variable were confirmed before the analyses using the Shapiro–Wilk test. One-way ANOVA was used to compare FMD among three occlusion pressures, while two-way repeated measured ANOVA within subjects was used for the pain and numbness scales. Bonferroni post hoc analysis was used to perform all pairwise comparisons between condition means. All p-values at 0.05 were considered to indicate statistical significance. All statistical procedures were performed using SPSS 17.0 (NY, USA). Partial Eta squared (η^2) were classified as small, medium, and large (0.01, 0.06, and 0.14, respectively) (Richardson, 2011).

RESULTS

Subject characteristics

Age, gender, weight, height, body mass index (BMI), systolic and diastolic blood pressure, resting heart rate, and physical activities are presented in Table 1.

Table 1. Subject characteristics.

Subject characteristics	Mean $\pm$ SD
Age (year)	28.08 $\pm$ 4.76
Gender (male/female)	50/50
Weight (kg)	64.28 $\pm$ 11.21
Height (cm)	168.42 $\pm$ 7.89
BMI (kg/m ²)	22.59 $\pm$ 3.09
Systolic blood pressure (mmHg)	118 $\pm$ 6.02
Diastolic blood pressure (mmHg)	79.33 $\pm$ 6.77
Resting heart rate (beats/min)	80.83 $\pm$ 13.76
Physical activity (METs/week)	1677 $\pm$ 1346

Note: Values are presented as means $\pm$ SD, with gender shown as a percentage.

Vascular parameters

There were no statistically significant differences in the baselines of vascular diameter ($F=0.319$, $P=0.73$), MBFVbase ($F=1.546$, $P=0.24$), MBFVpost ($F=2.180$, $P=0.14$), and the percentage change of FMD ($F=0.050$, $P=0.95$) between these three levels of occlusion pressure (Table 2).

Table 2. Flow-mediated dilation response before and after three levels of occlusion pressures.

Value	Occlusion Pressure			F test	P	η^2
	25 mmHg of supra SBP	50 mmHg of supra SBP	At 200 mmHg			
Baseline diameter (mm)	3.48 $\pm$ 0.62	3.46 $\pm$ 0.62	3.46 $\pm$ 0.67	0.31	0.73	0.28
Peak arterial diameter (mm)	3.84 $\pm$ 0.66	3.81 $\pm$ 0.70	3.79 $\pm$ 0.72	0.65	0.48	0.06
MBFVbase (cm/s)	2.63 $\pm$ 0.73	2.76 $\pm$ 0.85	2.84 $\pm$ 0.96	1.54	0.24	0.12
MBFVpost (cm/s)	11.52 $\pm$ 3.96	12.54 $\pm$ 4.31	12.28 $\pm$ 4.30	2.18	0.14	0.17
FMD (%)	10.11 $\pm$ 2.58	10.08 $\pm$ 2.7	10.15 $\pm$ 2.74	0.05	0.95	0.00

Note: Represented as means $\pm$ SD, s; second, η^2 ; partial Eta squared, cm; centimeter, mm; millimeter, mmHg; millimeter of mercury, FMD (%); percentage change of flow-mediated dilation, SBP; systolic blood pressure, MBFVbase; mean blood flow velocity at baseline, and MBFVpost; means blood flow velocity post occlusion.

Discomfort symptoms

Pain

During the 5-minute occlusion, the mean value of the pain scale of occlusion pressure at 25 mmHg, 50 mmHg, and 200 mmHg were 1.83 ± 0.98 , 2.34 ± 1.27 , and 3.63 ± 1.87 , respectively, while the maximum value of the pain scale of those mentioned pressures were 2.58 ± 0.59 , 3.42 ± 0.63 , and 5.08 ± 0.8 , respectively. After deflation, the pain scale of all different pressures remarkably decreased to lower than 3, gradually decreased, and disappeared within 3 minutes. Pain scale significantly interacted with the occlusion pressure and time ($F=1.79$, $p=0.016$). The main effects on the occlusion pressure ($F=3.56$, $P=0.039$) and time ($F=43.66$, $P<0.0001$) were significant for the pain scale. A significant difference was observed only in the pain scale between occlusion pressures of 25 mmHg and 200 mmHg at the time points of 1, 2, and 4 minutes (all $P<0.05$) (Figure 1).

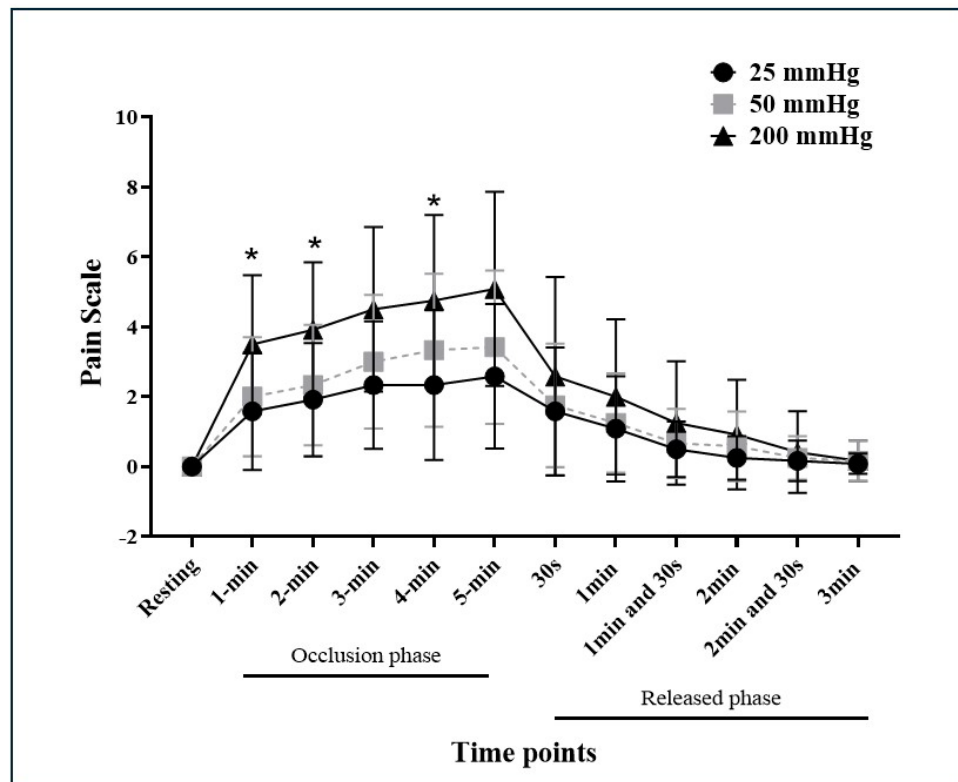


Figure 1. Pain scale for three levels of occlusion cuff pressures during the occlusion phase and released phase. * $P < 0.05$.

Numbness

During the 5-minute occlusion, the mean of the numbness scale of occlusion pressure at 25 mmHg, 50 mmHg, and 200 mmHg were 3.67 ± 2.02 , 4.24 ± 2.38 , and 4.72 ± 2.7 , respectively, while the maximum value of the numbness scale of those mentioned pressures were 5.3 ± 0.71 , 6.1 ± 0.59 , and 7.36 ± 0.59 , respectively. After deflation, the numbness scale gradually decreased from 6 to 0 within 5 minutes.

A significant main effect of time was observed for the numbness scale ($F=17.4$, $P < 0.0001$). There was no main effect of occlusion pressure on the numbness scale ($F=0.82$, $P=0.45$). The numbness scale insignificantly interacted with the occlusion pressure and time ($F=0.9$, $P=0.62$) (Figure 2).

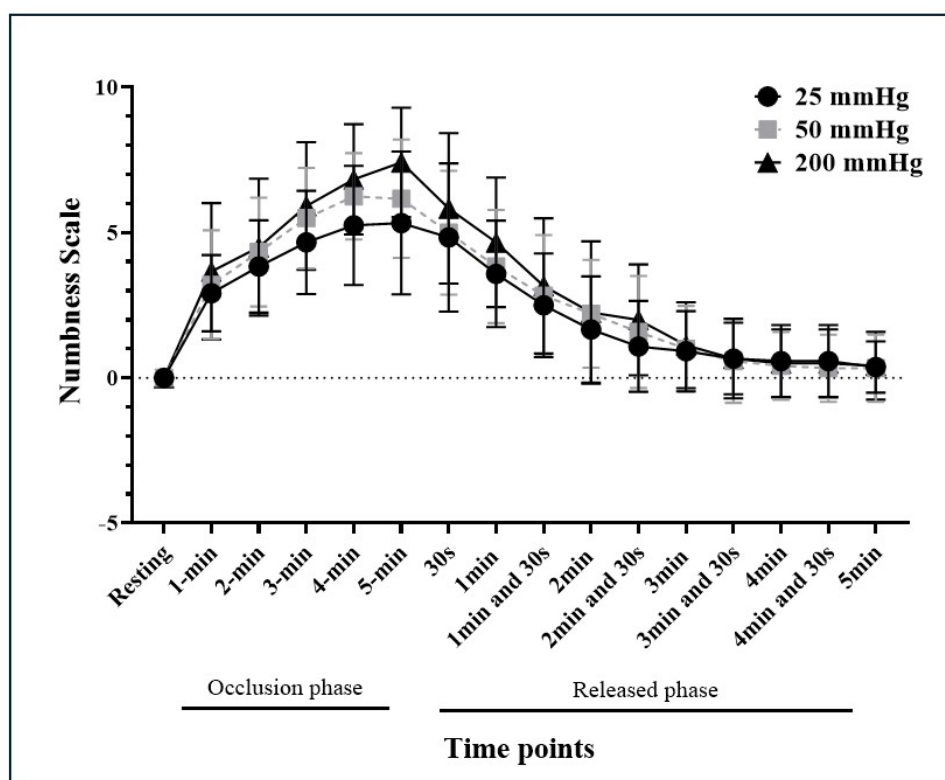


Figure 2. Numbness scale for three levels of occlusion cuff pressures during the occlusion phase and released phase. * $P < 0.05$.

DISCUSSION

The findings of this study demonstrated that an occlusion cuff pressure at 25 mmHg above SBP can induce mean values of %FMD and MBFVpost comparable to those of 50 mmHg above SBP and 200 mmHg. Notably, the pain sensation at a cuff pressure of 25 mmHg above SBP was significantly less than 200 mmHg during the first, second, and fourth minutes of cuff occlusion. The sensation of numbness was not affected by these occlusion cuff pressures.

Our findings align with those of previous study by McLay et al. (McLay, 2012), which found no significant differences in popliteal FMD measurements across five different occlusion pressures. In this study, the comparable results across pressure levels may be due to all the pressures used being above SBP. Such pressures are adequate to produce similar blood flow and shear stress, thereby inducing a NO response that causes vasodilation to a similar extent, as noted in previous research (Pyke and Tschakovsky, 2007; Thijssen et al., 2011). Additionally, our results support the majority of studies that used a cuff occlusion pressure of 200 mmHg or exceeding 50 mmHg above SBP, as per the expert consensus on FMD measurement (Thijssen et al., 2019). Importantly, we found that a cuff pressure of 25 mmHg above SBP is sufficient for measuring FMD in Thai adults.

Due to the lack of established reference ranges for FMD results, we compared the mean %FMD value of our participants to the reference value from Königstein et al. (2021), who used a cuff pressure of 50 mmHg above SBP (Königstein et al., 2021). Our findings showed a considerably higher %FMD value within the same age range. The high value can be considered normal, as an FMD value of less than 7.1% is used as a cut-off for diagnosing endothelial dysfunction (Maruhashi et al., 2020). Differences in ethnicity and geographical location between our participants and those in the Swiss study might account for these discrepancies. Another potential factor is

the difference in physical activity (PA) levels. Our participants engaged in more PA (>600 METs/week) compared to those in the Königstein et al.'s study, where 95% of participants had at least 150 minutes of moderate-to-vigorous physical activity per week, roughly equivalent to 500 METs/week. Given that physical activity is known to improve endothelial function and slow the progression of vascular changes (Pahkala et al., 2011; Kozakova et al., 2013), this higher level of PA may explain the elevated %FMD values observed in our study.

Research on pain perception, which may vary by ethnicity, has reported that Asian individuals are more sensitive to pain than Caucasians and African American individuals (Ramer et al., 1999; Rowell et al., 2011). This contrasts with earlier studies predominantly involving White populations, which reported minimal discomfort or complications, with only a few participants experiencing pain or numbness (Bots et al., 2005; Thijssen et al., 2011). In our study, we observed a significant difference in pain sensation during cuff occlusion. A pressure of 200 mmHg produced an average pain score of 4.4 on the NPRS, approximately twice as much as the pain experienced at 25 mmHg above SBP (with an average NPRS score of 2.2) over the 5-minute occlusion period. A change of 1.65-2.0 points on the NPRS is considered a minimal clinically important difference, reflecting a meaningful change in pain status (Bahreini et al., 2020; Suzuki et al., 2020).

Additionally, numbness, a loss of sensation due to blood flow restriction, was observed in our participants but did not differ significantly across the three pressure levels. Di Maio et al. reported that increased cuff pressure enhances nociceptor activation (Di Maio et al., 2023), resulting in more intense pain as the pressure rises. In contrast, Daly et al. explained that numbness occurs when sensory nerves involved in touch and proprioception are compressed (Daly et al., 2012). Once these nerves are sufficiently compressed, additional increases in pressure do not significantly alter the sensation of numbness, which explains why numbness did not change with different pressure levels in the present study. Overall, these results suggest that a higher cuff pressure of 200 mmHg induces more pain compared to a lower pressure of 25 mmHg above SBP for Thai participants, although both pressures produce similar %FMD results. Therefore, using a minimum occlusion pressure of 25 mmHg above SBP, which effectively stimulates the FMD response while minimizing pain, may be a more practical approach for FMD assessment in healthy Thai adults.

The strength of this study lies in its novel approach to compare different cuff occlusion pressures commonly used for measuring FMD in healthy adults, considering both endothelial response and discomfort levels, such as pain and numbness. However, it is important to note that the FMD procedure used in this study elicits only a reactive hyperemic stimulus, which is predominantly reflects endothelium-dependent and NO-mediated vasodilation, rather than endothelium-independent vasodilation. Additionally, habituation typically occurs with repeated stimuli without adequate rest (Rankin et al., 2009). In our study, we mitigated this by inducing discomfort through a single sustained stimulus during each occlusion. Discomfort subsided within 3-5 minutes post-deflation, followed by a 25-minute rest before the next trial. This 30-minute rest period minimized habituation effects, ensuring reliable results regarding unpleasant sensations and their impact on outcome measures (Rankin et al., 2009). This adequate rest interval is another strength of our study.

There are some limitations to this study. Firstly, the absence of lipid profile and glycemic index measurements, which can influence vascular function, is a notable limitation. However, the crossover design of the study mitigates these concerns to some extent. Secondly, the within-subject design could potentially lead to carryover effects. To address this, we randomly assigned the order of the pressure conditions and included 30-minute rest intervals between each condition to ensure that arterial data returned to baseline levels. Finally, the small effect size observed in %FMD suggests that a larger sample size is necessary for more robust and reliable results. Further studies are warranted to confirm these findings.

CONCLUSION

Occlusion cuff pressures at 25 mmHg above SBP induced brachial FMD responses similar to those at 50 mmHg above SBP and 200 mmHg, but with less pain. These findings suggest that 25 mmHg above SBP is a practical occlusion pressure for FMD assessment in healthy Thai adults.

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AUTHOR CONTRIBUTIONS

Study design and concept– Kanpiraya Nithitsuttibuta and Sainatee Pratanaphon; Study conduct and data collection– Kanpiraya Nithitsuttibuta and Jaruta Kunritt; Technical support for vascular assessment– Suchart Kiatwattanacharoen; analysis, interpretation, and drafted manuscript– Kanpiraya Nithitsuttibuta. and Sainatee Pratanaphon. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they hold no competing interests.

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