Relationship between Brachial pulse pressure index and subclinical atherosclerosis among susceptible individuals

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Abstract

Background: Atherosclerosis develops gradually with a subclinical change in arterial elasticity. Pulse pressure index (PPI) (i.e. pulse pressure/systolic blood pressure) could be a predictive parameter of decreased arterial compliance. **Objective:** This study aimed to evaluate whether brachial PPI (BPPI) is an independent predictor for increased Carotid intima-media thickness (CIMT), and additionally, whether BPPI is superior to brachial pulse pressure (BPP) in the prediction of subclinical atherosclerosis. **Methods:** In this cross-sectional study, 115 patients, aged 40-60 years, who attended Minia University Hospital Medical units, were recruited. Subjects who had a history of coronary heart disease or stroke or were prescribed to drugs that could affect blood pressure on the day of the study were excluded. CIMT at a cut-off value of > 0.9 mm was used as a reference measure. **Results:** The mean values of BPPI and BPP were 0.37±0.06 and 49.17±12.59, respectively. Subjects with BPPI ≥ 0.36 (median value) had higher CIMT (0.81±0.15 versus 0.72±0.14) compared to those with BPPI < 0.36. After multivariate analysis was completed, BPPI had significant correlation with CIMT (unstandardized coefficient β = 0.938, p < 0.001). The areas under the receiver operating curve for BPPI and BPP in the prediction of CIMT > 0.9 mm were 0.702 (p <0.001) and 0.598 (p =0.001), respectively. **Conclusion:** BPPI is a valuable predictive tool for subclinical atherosclerosis with higher predictive accuracy compared to BPP.
Keywords: Subclinical atherosclerosis; pulse pressure; pulse pressure index.

Introduction

Atherosclerosis is the underlying cause of heart disease and stroke. Importantly, atherosclerosis develops gradually as a subclinical condition and eventually becomes clinically apparent as heart disease or stroke (Zabalza et al., 2015). Cardiovascular disease (CVD) deaths account for approximately one third of all global deaths in 2016 and three quarter of all CVD deaths occurred in low- and middle-income countries (Ritchie & Roser, 2018). In Egypt, Ischemic heart disease and stroke remained the top causes of mortality for more than a decade and 8% of Egyptian population are at high risk for developing CVD (WHO, 2107).

There are several established procedures and methods for the early detection of subclinical atherosclerosis such as carotid intima-media thickness (CIMT), ankle-brachial index (ABI) and cardiovascular risk algorithms. However, all of them couldn't be used in routine clinical practice by every healthcare personnel as they require either particular equipment and a specialized user (Hietanen, Pääkkönen, & Salomaa, 2008) or invasive procedure (Filippi et al., 2016). As Nurses are more available to all populations compared with other health care personnel, the availability of an easily applied non-invasive non-user specific screening tool will greatly contribute for early prediction.

Blood pressure (BP) is a well-established risk factor for CVD risk in terms of systolic blood pressure (SBP) or diastolic blood pressure (DBP) (Miura et al., 2001; Sarafidis & Bakris, 2014). Pulse pressure (PP; calculated by SBP minus DBP) is also an independent predictor of coronary artery disease (CHD), heart failure, cerebrovascular disease among hypertensive subjects (Franklin, Khan, Wong, Larson, & Levy, 1999; Weitzman & Goldbourt, 2006). Although PP seemed to be beneficial in the evaluation of dynamic vascular compliance, there are major limitations of PP when applied in clinical practice. The first one that PP is easily alterable in the same individual and the other one is being irrelative to an absolute BP level. Besides, the speed of pulse waves depends not only on dynamic compliance but also on the intrinsic elastic properties and composition of the arterial wall (Marchais, Guerin, Pannier, Delavaud, & London, 1993).

Recently, based on the fluid-flow analog of Ohm's law and elastic chamber theory, Peng-Lin and Yue-Chun (2009) suggested a concept of pulse pressure index (PPI; calculated as PP/ SBP). Compared to PP, PPI can overcome the limitations of PP and reflect both dynamic and intrinsic vascular compliance. Consequently, PPI would be better than PP in the assessment of cardiovascular outcomes. Therefore, we conducted this study to evaluate whether BPPI is an independent predictor of increased CIMT, and additionally, whether Brachial PPI (BPPI) is superior to brachial PP (BPP) in the prediction of subclinical atherosclerosis.

Methods

Study design and population:

This cross-sectional study conducted on patients aged 40-60 and attended Minia University Hospital medical units, between July and November 2018. Subjects who had a history of coronary heart disease, stroke, peripheral vascular disease or were prescribed to drugs that could affect blood pressure reading on the day of the study were excluded. Atherosclerosis would be found after 40 years (Petisco et al., 2017) and a benign aging effect on CIMT would be found at the age of 60 years (Łoboz-Rudnicka et al., 2016). The protocol of the study was approved by the Ethics Research Committee of the Faculty of Nursing, Minia University, Egypt. All subjects were informed of the details of the study and signed their informed consent forms.

The number of subjects who provides the necessary sample size was 115 as calculated by (fisher et al, 1998) formula: $N = (z^2pq/e^2)$ (N = the required minimum sample size; p = the estimated proportion of atherosclerosis prevalence in the target population 8%; Q = 100 – P; e= acceptable error at 0.05; Z = the standard error (1.96) associated with the chosen level of confidence 95%).

Data collection:

BP was obtained from both arms according to the guideline's instruction using an electronic BP device while each subject was in a supine position (Dougherty, 2015). BP used for the data analysis was of the side of the maximum PP value in both arms. The fasting venous blood samples were drawn from each subject; then analyzed in the Research laboratory center at Minia University Hospital of Egypt.

A
B
C

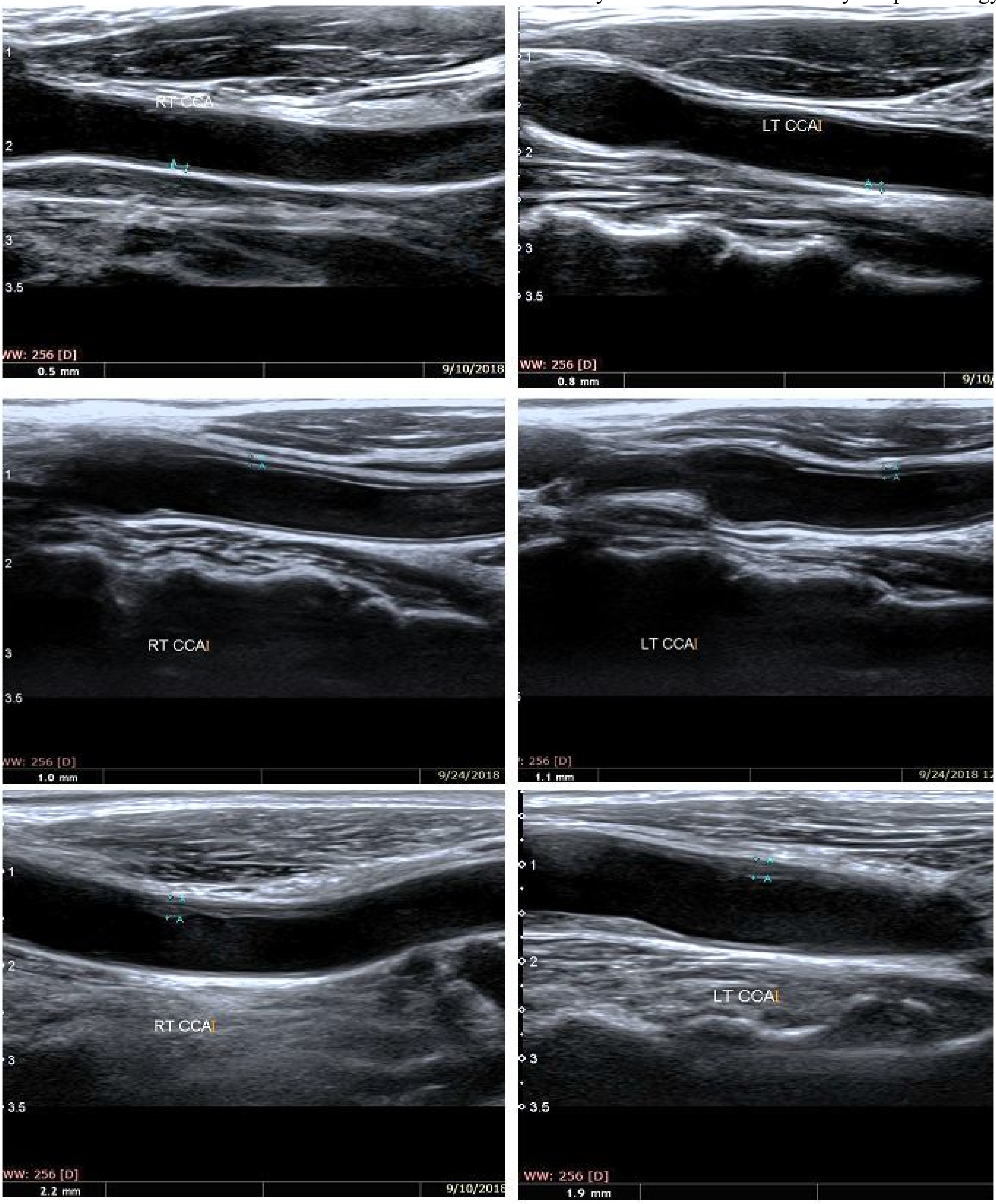

Figure1. High-resolution B mode Doppler ultrasonography of common carotid artery intima media thickness (CIMT) in 3 different cases (A, B and C). A: normal right (RT) and left (LT) CIMT (< 0.9 mm). B: a case of early atherosclerotic changes (RT CIMT= 1.0 mm, LT CIMT = 1.1). C: a case of suggested established bilateral carotid arterial atherosclerotic changes (RT CIMT= 2.2 mm, LT CIMT = 1.9).

Common carotid artery intima-media thickness (one millimeter below the carotid artery bifurcation) was measured by well-trained radiologists to evaluate subclinical atherosclerosis (20-year experience) using high frequency ultrasound machine (Toshiba Aplio 500, Japan). The value of CIMT was obtained with high-resolution B mode ultrasonography from both the right and the left common carotids and the average value between them was used for the presentation of the study analysis (Timóteo, Mota Carmo, Soares, & Ferreira, 2019) considering CIMT > 0.9 mm as abnormal (Simova, 2015) (figure1). CIMT has been recommended by the US Food and Drug Administration for screening early atherosclerosis, especially in people at intermediate risk (Yokoi et al., 2014).

To calculate intra-observer and inter-observer variation; CIMT measurement was repeated by the same radiologist and another one in two subsamples of the study subjects consisted of 30 subjects in each. The interclass correlation coefficients for intra-observer and inter-observer reproducibility were 0.96 (95% confidence interval (CI) 0.94 to 0.97, p< 0.05) and 0.95 (95% CI 0.93 to 0.96, p < 0.05), respectively, which means good agreement beyond chance (Hallgren, 2012).

Statistical Analyses:

Characteristics of the study subjects and comparison of characteristics according to high and low BPPI (divided by the median value) were performed. The Continuous variable was presented as mean ± standard deviation and compared by independent t-test when data were normally distributed, otherwise compared by Wilcoxon rank-sum test. Categorical data were presented as a number and percentage and compared by the Chi-squared test. Pearson's moment correlation was conducted to show the relation between CIMT and BP indices. Then, we adjusted the BPPI for the following variables; age (years), sex (male or female), body mass index (BMI) (kg/m2), smoking habit (current or not), diabetes mellitus (yes or no), family history of vascular events (yes/no), sleep (hours/day) and 30 exercise/day (>5 times/week or less), perceived feeling of moderate to severe stress (yes/no) and total cholesterol (mg/dl). We tested the multicollinearity by calculating the variance inflation factor (VIF) and revealed no multicollinearity in multiple regression analyses models. The receiver operating characteristic curve (ROC) was used to evaluate the significance of BPPI and BPP in the prediction of CIMT. Statistical analyses were performed by using SPSS software version 21.0. A difference was considered significant if the p-value was < 0.05.

Results

Table 1. Comparison of baseline characteristics according to median value of BPPI (0.36 ±0.06):

	BPPI<0.36 n=57	BPPI ≥ 0.36 n=58	P-value	Total N=115
Age (years) [a]	48.49±4.57*	51.26±4.16	0.001	49.89±4.57
Male, n (%)	28 (49.1%)	33(56.9%)	.404	61(53.0%)
Current smoker, n (%)	13 (22.8%)	7 (12.1%)	.129	20(17.4%)
Perceived feeling of stress, n (%)	10 (17.5%)*	20 (34.5%)	.039	30 (26.1%)
Exercise >5 times/week, n (%)	20(35.1%)	11(19.0%)	.051	31(27%)
DM, n (%)	14(24.6%)	17(29.3%)	.566	31(27.0%)
HTN, n (%)	25 (43.9%)	32(55.2%)	.225	57(49.6%)
Anaemia, n (%)	8 (14.0%)*	2 (3.4%)	.044	10 (8.7%)
Family history of CVD event [b], n (%)	0 (0.0%)	2 (3.4)	0.157	2 (1.7%)
BMI (kg/m^2) [a]	37.22±7.82	38.93±9.17	0.284	38.09±8.53
Sleep hours/ day[a]	6.95±1.74	7.24±1.95	0.396	7.1±1.84
TC (mg/dl) [a]	182.32±39.97	190.46±42.67	.294	186.42±41.37
HbA1c (mg/dl) [a]	5.55±1.04*	6.69±2.11	<0.001	6.12±1.76
SBP (mmHg) [a]	126.23±17.33*	136±19.54	.005	131.16±19.04
DBP (mmHg) [a]	85.26±11.24*	78.95±10.2	.002	82.08±11.14
pulse (beats/minute) [a]	79.25±12.47	78.76±11.39	.827	79±11.89
PP (mmHg) [a]	40.96±7.08*	57.22±11.6	<0.001	49.17±12.59
PPI [a]	0.32±0.02*	0.42±0.04	<0.001	0.37±0.06
CIMT (mm) [a]	0.72±0.14*	0.81±0.15	0.002	0.77±0.15

*** p < 0.05,** [a]Mean ± SD (all such values), [b] CVD event: coronary heart disease or stroke.
BMI, body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; PP, pulse pressure; PPI, pulse pressure index; TC, total cholesterol; SBP, systolic blood pressure.

There were 115 subjects with a mean age of 49.89±4.57 years, and 53.0 % of them were male. Mean values of BPPI and BPP were 0.37±0.06 and 49.17±12.59, respectively. Mean BMI was 37.76±8.65 kg/m2 and approximately 32.8% of the men subjects were smokers. Table 1 shows the comparison of baseline characteristics between two groups (high BPPI ≥ 0.36 versus low BPPI < 0.36) divided by median BPPI. Subjects of high BPPI group had higher proportions of diabetic, hypertensive and older adult subjects. In comparison to the low BPPI group; SBP, PP, CIMT, serum and total cholesterol were higher in the high BPPI group, whereas DBP and pulse were lower. Mean CIMTs were 0.81±0.15 mm and 0.72±0.14 mm in the high BPPI group and low BPPI group, respectively.

Table 2. Pearson moment correlation between brachial blood pressure indices and carotid intima-media thickness:

	r	p-value
Systolic blood pressure	0.021	0.826
Diastolic blood pressure	-.260*	0.005
Pulse pressure	0.270*	0.004
Pulse pressure index	0.425*	<.001

*** p < 0.05**

Table (2) show that DBP was negatively associated with CIMT by Pearson's correlation. (r=-.260, P<0.05) while BPP and BPPI were positively associated (BPP; r=0.270, P=0.004 and BPPI r=0.0.425, P<0.001).

Table 3. Multiple linear regression analysis for the association between brachial pulse pressure index and carotid intima-media thickness in different models:

	β (95% CI)	SE	t	P-value
Model 1	1.103 (.665-.1.540)	.221	4.989	<0.001
Model 2	.904 (.464-.1.345)	.222	4.065	<0.001
Model 3	.911 (.470-1.352)	.223	4.091	<0.001
Model 4	.938 (.522-1.355)	.210	4.472	<0.001

Model1: adjusted for brachial pulse pressure index. Model 2: further adjusted for age (years). Model 3: further adjusted for sex (male, female). Model 4: further adjusted for smoking cigarette (ever, never), diabetes mellitus (yes, no), family history of stroke or coronary heart disease (yes, no), body mass index (Kg/m2), total cholesterol level(mg/dl), vigorous exercise >5 times/week (yes/no), perceived feeling of stress (no to mild, moderate to severe), and sleep hours per day. β, unstandardized coefficient, represents the degree of change in Carotid intima-media thickness in ml and t.values per one standard deviation of brachial pulse pressure index.

Table (3) conclude that after adjusting for age, sex, smoking, diabetes, BMI, serum total cholesterol, exercise, sleep hours/day and stress, BPPI had a significant correlation with CIMT (unstandardized coefficient β = 0.938, p < 0.001).

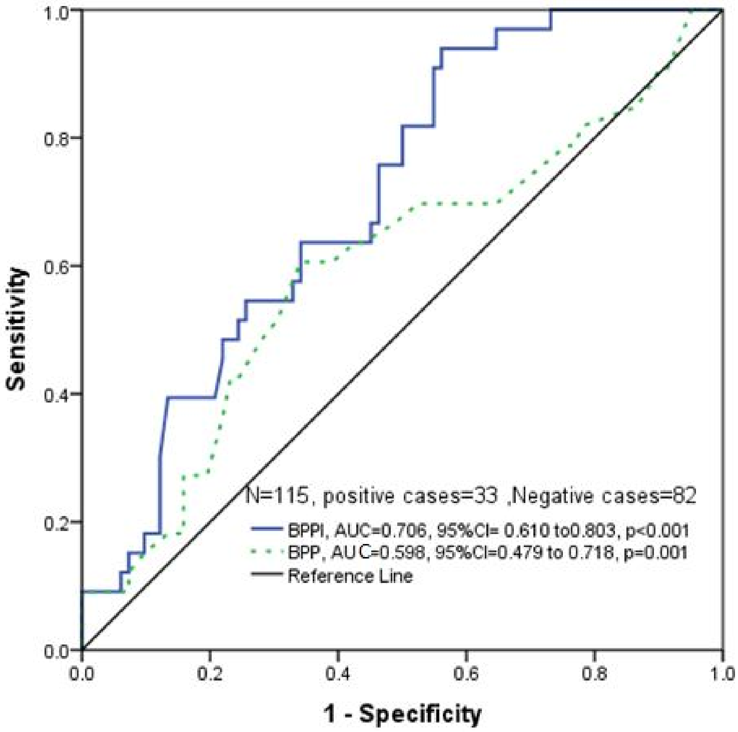

Figure 2. The areas under the receiver operating characteristic curves (AUCs) and corresponding confidence interval (CI) for brachial pulse pressure (BPP) and brachial pulse pressure index (BPPI) in the prediction of carotid intima-media thickness > 0.9 mm.

The ROC evaluations showed that areas under the curve (AUC) for BPP and BPPI to predict CIMT increase were 0.598 ± 0.061 (p=0.001) and 0.702 ± 0.049 (p<0.001), respectively (figure2)

Discussion

The main finding of our study that BPPI was an independent predictor of subclinical atherosclerosis with higher predictive capacity than BPP. Furthermore, this association remained significant even after controlling for age, sex, smoking BMI, serum total cholesterol, diabetes, family history of vascular events, sleep hours per day and exercise.

These results suggested that BPPI contributes significantly to CIMT augmentation which is a predictor of atherosclerotic vascular diseases. Increased CIMT in the common carotid segment is linked to a yearly risk of 0.7% to 2.2% in coronary heart disease, 0.4% to 1.8% in cerebrovascular stroke and 1.8% to 3.2% in total cardiovascular diseases (Saedi, Ghadrdoost, Pouraliakbar, Zahedmehr, & Jebelli, 2018).

Prior studies of Chinese populations have shown that brachial PPI is significantly associated with the renal resistive index, renal function and left ventricular diastolic dysfunction (M.-K. Lee et al., 2015). Cai et al. (2015) conducted an observational study to investigate the relationship among brachial PP, brachial PPI, and CIMT in 342 Chinese adults newly diagnosed as hypertensive without anti-hypertensive therapy and aged 63.0 ± 11.4 years. Only brachial PPI was an independent determinant for CIMT increase after adjusted for the traditional risk factors and the ROC evaluations showed that AUC for BPP to predict CIMT increase was 0.591 ± 0.034 while BPPI was 0.664 ± 0.033. Similarly, our findings revealed that AUCs of BPP and BPPI to predict CIMT increase were 0.598± 0.049 and 0.702± 0.061, respectively and BPPI has a significant relation even after adjusted with other risk factors.

As aforementioned, PPI is calculated by PP divided by SBP. Based on the elastic chamber theory, the formula of PPI calculation can be changed into as follow: PPI=pulse pressure/systolic pressure=(Cs-Cd)/(Cs-C0), in which Cs, Cd, and C0 refer to the arterial compliance at SBP, DBP, and zero-pressure, respectively. The value of PP represents the dynamic compliance whereas the value SBP reflects the arterial intrinsic compliance (Peng-Lin & Yue-Chun, 2009). Regarding

The magnitude of BPPI would be determined by the interaction of the incident pressure wave generated by left ventricular ejection and reflected wave(s) generated by the arterial system. Changes in arterial compliance affect the timing of the incident and reflected waves to the heart (Hickson et al., 2016). When arterial compliance is decreased, pressure waves are more rapidly propagated along the arteries and return to the heart from reflective sites before ventricular ejection has ceased. As a result, the early return induces an increase in systolic pressure, and a decrease in diastolic blood pressure (Marchais et al., 1993). Thus, the decreased arterial compliance could be represented by the increased proportion of PP form the total systolic BP (i.e. PPI) which may be caused by either increased systolic BP or decreased diastolic BP or both.

Consequently, the subsequent rise in systolic pressure increases myocardial oxygen uptake, while the reduction in diastolic pressure induces a decreased coronary blood flow. The increase in SBP also increases ventricular afterload, altering the ventricular ejection and resulting in left ventricular hypertrophy. Accordingly, BPPI will reflect both dynamic and intrinsic compliance and would be a predictor of adverse cardiovascular outcomes (Berne & Levy; Peng-Lin & Yue-Chun, 2009; Safar, Blacher, & Jankowski, 2011). Accordingly, a study of W.-H. Lee et al. (2013) revealed that after control for other variables including PP, increased PPI was still significantly associated with left ventricular diastolic dysfunction. other studies conducted among Chinese and also demonstrated that PPI had a significant association with atherosclerosis and cardiovascular event (Cai et al., 2015; Zhang et al., 2007; Zhao, Shen, Wang, LIN, & ZHAO, 2007).

In comparison to all well-established tools and procedures which predict subclinical atherosclerosis, BPPI can serve as a non-invasive, operator-independent preliminary screening parameter and can be rapidly obtained by an electronic device in daily clinical practice by every health care personnel.

Limitation of the study:

Our study has some limitations. First of all, our current study was an observational cross-sectional study so that the causality assumption is violated. Second, the small sample size of our current study. Third, some of the hypertensive subjects were treated chronically with antihypertensive medications and ethically we did not withdraw them from these medications.

Conclusion

In conclusion, the present study demonstrated that BPPI was an independent predictor of CIMT measured with high-resolution B mode Doppler ultrasonography. Importantly, BPPI has a powerful capacity to discriminate CIMT increase with better accuracy than BPP. Hence, nurses and other health care provider can use BPPI as a preliminary screening tool for subclinical atherosclerosis as BPPI would be an alarm sign for those who have already developed arterial impairment. However, the clinical application of BPPI needs further studies.

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