Full title   Postprandial hypertension, an overlooked risk marker for arteriosclerosis

Short title   postprandial hypertension, arteroscrerosis and insulin resistance

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ABSTRACT

Objective: Increased blood pressure (BP) variability is suggested to be a risk factor for cardiovascular disease. Although a postprandial decline in BP is a frequently observed phenomenon in the elderly, little attention has been paid to the clinical and diagnostic significance of postprandial BP change. Here, we aimed to clarify the possible association between postprandial BP dysregulation and arteriosclerosis.

Methods: The study subjects were 1,339 apparently healthy middle-aged to elderly persons (66±9 years old). Postprandial changes in BP were calculated by two readings on the same day, one just before lunch with a standardized Japanese meal and the second 30 min after lunch. Arteriosclerosis was assessed by carotid intima-media thickness and brachial-to-ankle pulse wave velocity.

Results: Mean preprandial and postprandial systolic BP was 127±18 and 123±18 mmHg respectively. One hundred and twelve subjects (8.4%) showed a greater than 20-mmHg postprandial decline in systolic BP, while 129 (9.6%) showed a greater than 10-mmHg increase. Arteriosclerosis was significantly higher in both postprandial hypotensive and hypertensive subjects. The postprandial changes in systolic BP was strongly associated with preprandial systolic BP (r=0.335, p<0.001). The association between postprandial hypotension and increased arteriosclerosis was therefore lost after adjustment for basal systoic BP. Multiple linear regression analysis adjusted for possible covariates, including basal BP, identified a postprandial increase in BP as an independent determinant of insulin resistance as assessed byHOMA-IR (β=0.093, p<0.001), carotid thickness (β=0.086, p=0.001) and pulse wave velocity (β=0.170, p<0.001).

Conclusion: Postprandial increase in BP is a novel risk marker for arteriosclerosis.

INTRODUCTION

Blood pressure dysregulation in the elderly is a known risk factor for cardiovascular disease and mortality. Orthostatic hypotension is a well-investigated phenomenon that has been postulated to be associated with cerebrovascular [1] and cardiovascular disease [2, 3], as well as mortality [4, 5]. Arterial stiffness and a consequent attenuation of baroreceptor response to orthostatic stimuli is thought to be an underlying mechanism relating orthostatic hypotension and cardiovascular organ damage [6-8]. In addition to a postural blood pressure (BP) decline, we previously reported that orthostatic increases in BP also reflect arterial stiffening [9]. Associations between orthostatic hypertension and silent cerebral infarction have also been reported in hypertensive subjects [10].

Postprandial hypotension (PHYPO) is another BP instability that is frequently observed in elderly people [11-13]. A limited number of studies has indicated that PHYPO increases the risk of cardiovascular disease [14], asymptomatic cerebrovascular damage [15], stroke [14], and mortality [16]. However, sample size of these studies was small, and the subjects were frail elderly or subjects with hypertension. Rather, a comprehensive understanding of the association between PHYPO and cardiovascular risks requires epidemiological studies in general populations. Further, no studies have focused on the prognostic or diagnostic significance of postprandial hypertension (PHT). Given that both orthostatic increases and decreases in BP increase the risk of cardiovascular disease [9, 10], it is possible that not only PHYPO but also PHT predict arterosclerotic vascular change.

To investigate this idea, we investigated the association of postprandial changes in BP with insulin resistance, carotid intina-media thickness (IMT), and pulse wave velocity in apparently healthy community-dwelling middle-aged to elderly subjects.

SUBJECTS AND METHODS

Study subjects

The study subjects were 1,339 apparently healthy middle-aged to elderly persons who were consecutive participants in the medical check-up program at Ehime University Hospital Anti-aging Center from February 2006 to March 2011. This medical check-up program was specifically designed to evaluate aging-related disorders, including arteriosclerosis, cardiovascular diseases (CVD) and physical function [17, 18]. Persons with any history of symptomatic cerebrovascular events, including transient ischemic attack , coronary heart disease and congestive heart failure, were excluded from the analysis. All participants were physically independent and completed all clinical measurements. The series of studies of which the present study was approved by the ethics committee of Ehime University Graduate School of Medicine.

Measurement of BP and augmentation index (AIx)

Brachial BP and radial arterial waveform were measured simultaneously (HEM-9000AI; Omron Healthcare, Kyoto, Japan) after 5 min rest in the sitting position. Briefly, brachial BP was measured on the right upper arm using a cuff-oscillometric device, and the radial arterial waveform was simultaneously obtained from the left wrist using a multi-element tonometric sensor. Radial AIx was obtained from the waveform as the ratio of the height of the late systolic peak to that of the first peak (Supplemental Figure 1). The AIx measurement has been briefly described elsewhere [19]. Subjects with any or all of a systolic BP (SBP) of ≥140 mmHg, diastolic BP (DBP) ≥90 mmHg, or the use of antihypertensive medication were regarded as having hypertension.

Evaluation of postprandial BP change

Postprandial changes in BP were calculated from two readings in a single day, one obtained

just before lunch and the second at 30 min after lunch. In the both measurements, single

reading was obtained. Postprandial BP change was calcurated by subtracting preprandial SBP

from postprandial SBP. Subjects were classified into four groups according to postprandial

change in SBP (ΔSBP) (Supplemental Figure 2): postprandial hypotension-2 (PHYPO-2:

n=112, ΔSBP$\leq$−20 mmHg), PHYPO-1 (n=244, -20<ΔSBP$\leq$−10 mmHg), Control (n=854,

-10<ΔSBP$\leq$10 mmHg), and postprandial hypertension (PHT: n=129, ΔSBP >10 mmHg).

Lunch consisted of a standardized traditional Japanese meal (600 kcal) for all subjects.

Ambulatory BP monitoring

Ambulatory BP was monitored in 588 subjects within one week from the medical check-up. A

fully automatic cuff-oscillometric device (TM-2431, A&D Co. Inc., Tokyo, Japan) which was

pre-set to measure BP and heart rate every 15 min during the day (7 AM to 10 PM) and every

30 min at night was used to measure ambulatory BP. Outliers of ambulatory BP reading were

rejected using the A&D method, the most widely used simple rejection method that excludes

BP readings outside a specified range [20]. Sleep duration was assessed by individual

interview, and overall average 24-h awake ambulatory BP values were calculated for each

individual.

Evaluation of carotid arteriosclerosis

Ultrasonography of the common carotid artery was performed using an SSD-3500SV or α10

ultrasonograph (Aloka Co, Ltd., Tokyo, Japan) with a 7.5-MHz probe [21]. After 10 min rest

in the supine position, optical visualization of the bilateral carotid arteries was obtained with

the subject's head tilted slightly upward in the mild-line position. IMT of the far wall was

measured from B-mode images using built-in computerized software, which simultaneously

measured IMT at three points with 1-cm intervals. Nine IMTs of the far wall were measured

at 1-cm interval proximal to the bulb from the anterior, lateral and posterior approaches. Mean

IMT calculated from the nine readings was used in the analysis. No measurements were taken at the level of a discrete plaque.

Measurement of brachial-to-ankle pulse wave velocity

Brachial-to-ankle pulse wave velocity (baPWV) was measured as an index of arterial stiffness. To measure baPWV, cuffs were applied to both brachia and ankles, and all blood pressures (BPs) were measured simultaneously by the cuff-oscillometric method (BP-203RPEII (form PWV/ABI), Omron Healthcare). The pulse volume waveforms were also recorded simultaneously using a plethymographic sensor connected to the cuffs. baPWV was calculated from the time interval between the wave fronts of the brachial and ankle waveforms, and the path length from the brachial to ankle. All measurements were performed in the supine position after at least 5 min rest. A brief explanation of this device as well as the validity and reproducibility of its measurements have been provided elsewhere [22].

Risk factor evaluation

Clinical data used in this study were obtained from the personal health record evaluated at the medical check-up program. Venous blood was collected in the morning after a 12 h fast. The homeostasis model assessment index for insulin resistance (HOMA-IR) was used as an index of insulin resistance, namely immunoreactive insulin (μU/ml) $\times$ glucose (mg/dl)/405. Type 2 diabetes was defined as any or all of a fasting plasma glucose level of $\geq$126 mg/dl, HbA1c $\geq$6.5%, or use of medication to lower blood glucose levels.

Statistical analysis

Differences in numeric variables were assessed by analysis of variance (ANOVA), while frequency differences were assessed using a chi-squared test. Multiple linear regression analysis was used to identify factors independently associated with baPWV, carotid IMT and

HOMA-IR. HOMA-IR was log-transformed in the multiple linear regression analysis. All statistical analyses were conducted using commercially available statistical software (JMP; SAS Institute Inc., Cary, NC), with p-values less than 0.05 considered statistically significant.

RESULTS

Clinical characteristics of the study subjects are summarized in Table 1. A total of 44.5% subjects were diagnosed as having hypertension, of whom 69.2% were taking antihypertensive medication.

Mean postprandial SBP, DBP and HR were 123 ± 18, 67 ± 11 mmHg and 71 ± 11 beats/min respectively. Changes in SBP (-4 ± 11 mmHg), DBP (-6 ± 6 mmHg) and HR (5 ± 5 beats/min) were significantly correlated with those in preprandial pressures (ΔSBP, r=-0.335 (Supplemental Figure 3), p<0.001; ΔDBP, r=-0.302, p<0.001; ΔPR, r=-0.216, p<0.001).

Associations of a postprandial SBP change with baPWV and carotid IMT are shown in Figure 1A and 1C, respectively. There were significant and J-shaped relationships between these parameters, with both PHYPO and PHT subjects having a higher baPWV and carotid IMT. Subjects categorized in the PHYPO groups (PHYPO-1 or PHYPO-2) were older and had higher preprandial BPs (Table 2). Further, the proportion of hypertension was particularly high in the PHYPO-2 group (p<0.001) (Figure 2), whereas the ratio of continuous hypertensive subjects taking antihypertensive medication was obviously lower in this group (PHYPO-2, 35.4%; PHYPO-1, 59.7%; Control, 77.3%; PHT, 85.1%; p<0.001). Other distinctive features of the PHYPO groups were a high preprandial AIx and a large postprandial change in AIx (Table 2). Given these results, the large blood pressure drop in postprandial hypotensive subjects may be largely attributed to a high preprandial blood pressure resulting from the white coat effect. Actuarlly, the J-shapes associations observed in the former simple comaarison (Figure 1A and 1C) became linear after adjustment of covariates, including preprandial BP (Figure 1B and 1D). The higher baPWV and carotid IMT

in the PHYPO subjects might have been augmented by basal BP. This possibility is supported

by the lack of association in ambulatory BPs between the control and PHYPO groups

(Supplemental Figure 4). In contrast, the PHT subjects were likely to be obese and had higher

HOMA-IR and plasma insulin levels (Table 2).

Factors independently associated with arterial parameters were identified using

multiple linear regression analysis (Table 3). Results showed that a postprandial change in

SBP was an independent and positive determinant of arterial parameters, namely baPWV and

carotid IMT, as well as insulin resistance, even in the analyisis adjusted mean BP instead of

SBP (carotid IMT, $p=0.033$; baPWV, $p<0.001$; HOMA-IR, $p=0.001$). We further conducted

sub-analysis stratified by hypertension status. Associations between postprandial changes in

SBP and arterial parameters were somewhat prominent in normotensive persons (carotid IMT,

$p=0.002$; baPWV, $p<0.001$; HOMA-IR, $p=0.022$) rather than hypertensive subjects (carotid

IMT, $p=0.110$; baPWV, $p<0.001$; HOMA-IR, $p=0.002$).

Finaly, we investigated a class-effect of antihypertensive drugs. In the regression

model adjusted for basal SBP, use of calcium-channel blockers (19.4% of total subjects,

$p<0.001$), alpha-blockers (0.8%, $p=0.010$), and diuretics (1.9%, $p<0.001$), but not

beta-blockers (3.1%, $p=0.159$) and angiotensin II receptor blockers (14.1%, $p=0.213$), were

positively associated with postprandial changes in SBP. However, associations between

postprandial SBP change and arterial parameters were independent of antihypertensive

medications (carotid IMT, $p<0.001$; baPWV, $p<0.001$; HOMA-IR, $p<0.001$).

DISCUSSION

In this study, we showed that PHT was a significant risk marker for arteriosclerosis in elderly

community residents. While both PHT and PHYPO showed significant associations with

arteriosclerosis in a simple correlation analysis, only PHT showed an increased risk in the

covariate-adjusted analysis.

Postprandial hypotension is frequently observed in elderly persons. In this study, 26% of subjects showed a greater than 10-mmHg decline in SBP after a meal. One plausible reason for this postprandial BP drop is an inadequate compensatory response for the physiological postprandial decrease in BP due to a blunted sympathetic response [12]. In contrast, no study has focused on PHT. In healthy elderly, postprandial BP is maintained by increases in heart rate, vascular resistance, and cardiac output [23], suggesting sympathetic hyperactivity as a plausible explanation for PHT. The PHT subjects in this study had a higher incidence of obesity and diabetes, and higher basal BP than those without this condition. The reportedly higher sympathetic reactivity in persons with obesity [24], type 2 diabetes [25], and essential hypertension [26, 27] suggest that these causes of arteriosclerosis may be associated with PHT and increased baPWV, as well as with IMT.

PHYPO has been suggested to be a risk factor for cardiovascular disease [14-16]. In this study, although we observed higher baPWV and carotid IMT in the PHYPO subjects, the association was lost after adjustment for covariates, particularly basal BP. Further, adjusted mean carotid IMT and baPWV of the PHYPO-2 group were lowest among the four subgroups. Since a postprandial BP decrease was partially dependent on preprandial BP, the larger BP decrease in the PHYPO subjects might be attributable to their higher basal BP. However, the frequency of patients with essential hypertension taking antihypertensive medication was lower in the PHYPO groups, suggesting the white-coat effect as a cause of the high basal BP in the PHYPO subjects. More profound postprandial declin in AIx against an increased symapathetic activity after meal (Supplemental Figure 4), as well as the average levels of ambulatory measured awake SBP (Supplemental Figure 5), in the PHYPO groups support this consideration. White-coat hypertension has been identifed as a potential risk for cardiovascular disease [28, 29]. Given these results, a postprandial BP decline may not itself be a risk marker for arteriosclerosis in healthy elderly. Previous reports, including ours, that reported an increased risk of postprandial hypotension were based on care residents [14, 16]

or hospitalized patients [15]. Further, we used ambulatory BP monitoring to evaluate the postprandial decrease in BP [15]. The white-coat effect might not arise under this condition and accordingly have no substantial impact on the evaluation of postprandial BP drop. The prognostic and diagnostic significance of postprandial hypotension in healthy elderly warrant further investigation.

Orthostatic BP dysregulation is another phenomenon suggested to be a cardiovascular risk [1-5, 9]. Although orthostatic BP change is simply measured within a few minutes, it is a highly complex phenotype affected by many factors relating to postural change. Compared with orthostatic stimuli, the effect of a meal on BP appears easy to evaluate, simply by two measurements of BP while seated. We therefore speculate that postprandial BP change is more reproducible than orthostatic BP change, albeit that no studies, including ours, have investigated the reproducibility of postprandial BP change. This issue warrants mention as a limitation of our study.

A postprandial increase but not decrease in BP is a novel marker for arteriosclerosis in healthy community elderly. Accumulated evidence has suggested that an increase in BP variability reflects cardiovascular risk. We should recognize excessive postprandial BP change as a phenotype of BP variability resulting from cardiovascular frailty. A comprehensive understanding of the prognostic significance of postprandial BP variability awaits a number of studies.

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FIGURE LEGENDS

Figure 1 Associations between postprandial change in SBP and arterial stiffness.

Subjects were classified into four groups according to postprandial change in SBP: postprandial hypotension-2 (PHYPO-2: ΔSBP$\leq$-20 mmHg), PHYPO-1 (-20<ΔSBP$\leq$-10 mmHg), Control (-10<ΔSBP$\leq$10 mmHg), and postprandial hypertension (PHT: ΔSBP >10 mmHg). The number of subjects in each subgroup is shown in the column. Figure 1A and 1C: crude mean ± standard deviation; Figure 1B and 1D: adjusted mean ± standard error calculated by multiple regression analysis adjusted for age, sex, BMI, HOMA-IR and preprandial SBP.

Figure 2 Proportion of hypertensive subjects

Subjects were classified into four groups according to postprandial change in SBP: postprandial hypotension-2 (PHYPO-2: ΔSBP$\leq$-20 mmHg), PHYPO-1 (-20<ΔSBP$\leq$-10 mmHg), Control (-10<ΔSBP$\leq$10 mmHg), and postprandial hypertension (PHT: ΔSBP >10 mmHg). Hypertension was defined as a SBP equal to or greater than 140 mmHg or a DBP equal to or greater than 90 mmHg. Frequency difference was assesed by chi-squared test.

Table 1 Clinical characteristics of study subjects (n=1,339)

Age (years)	66.2±8.9
Male (%)	38.7
Body mass index (kg/m²)	23.2±3.1
Obesity (obesity/over weight/normal weight)	22/334/983
SBP (mmHg)	127±18
DBP (mmHg)	72±11
HR (beats/min)	66±10
Antihypertensive medication (%)	30.8
Hypertension (%)	44.5
Glucose (mg/dl)	104±18
Type 2 diabetes (%)	10.4
Antihyperglycemic medication (%)	6.1
Total cholesterol (mg/dl)	219±36
HDL cholesterol (mg/dl)	68±19
Triglyceride (mg/dl)	107±58
HOMA-IR	1.52±1.22
Carotid IMT (mm)	0.80±0.16
baPWV (cm/sec)	1591±331

Values are mean±standard deviation. The homeostasis model assessment index for insulin resistance (HOMA-IR) was calculated using the following formula; immunoreactive insulin (μU/ml) × glucose (mg/dl)/405. Intima media thickness (IMT) at the common carotid artery was measured by ultrasonography. Brachial-to-ankle pulse wave velocity (baPWV) was calculated from the time interval between the wave fronts of the brachial and ankle waveforms, and the path length from the brachial to ankle. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Obesity was defined as follows; obesity, BMI ≥30 kg/m^2; over weight, 29>BMI≥25 kg/m^2; noraml weight, BMI<25 kg/m^2.

Table 2 Characteristic of subjects by postprandial change in SBP

		PHYPO-2 (n=112)	PHYPO -1 (n=244)	Control (n=854)	PHT (n=129)	p
Age (years)		69.7±7.2	67.0±8.2	65.5±9.2	66.5±8.6	<0.001
Male (%)		42.0	32.8	39.9	38.8	0.200
Obesity (obesity/over weight/normal weight)		0/22/90	4/47/193	13/227/614	5/38/86	0.020
Insuin (μU/ml)		1.37±1.33	1.36±0.97	1.54±1.21	1.83±1.49	0.002
HOMA-IR		5.06±2.87	5.28±3.06	5.86±3.92	6.75±4.97	0.001
SBP (mmHg)	preprandial	146±17	132±18	123±17	124±16	<0.001
	postprandial	121±17	118±18	123±17	139±17	<0.001
	ΔSBP	-26±6	-14±3	-1±5	16±5	<0.001
DBP (mmHg)	preprandial	79±12	75±11	71±10	71±11	<0.001
	postprandial	65±12	65±11	67±10	72±12	<0.001
	ΔDBP	-14±5	-9±5	-4±5	2±5	<0.001
HR (beats/min)	preprandial	64±10	67±11	66±10	67±11	0.053
	postprandial	70±11	72±11	71±10	71±12	0.146
	ΔPR	6±5	5±5	5±5	5±6	0.060
AIx at PR 75 betas/min (%)	preprandial	89±10	87±10	84±11	85±11	<0.001
	postprandial	79±12	80±12	79±12	83±12	0.011
	ΔAIx	-10±9	-7±10	-5±9	-2±10	<0.001

Values are mean±standard deviation. Blood pressure (BP), heart rate (HR) and augmentation index (AIx) were measured in the sitting position after more than 5 min rest using a standard automatic cuff-oscillometric device. The augmentation index was adjusted for HR at 75 beats/min. Postprandial changes in BPs, HR and AIx were calculated from two readings, one obtained just before lunch and the second 30 min after lunch. Subjects were classified into four groups according to postprandial change in SBP: postprandial hypotension-2 (PHYPO-2: ΔSBP≤−20 mmHg), PHYPO-1 (-20<ΔSBP≤−10 mmHg), Control (-10<ΔSBP≤10 mmHg), and postprandial hypertension (PHT: ΔSBP >10 mmHg). DBP: diastolic BP. Obesity was defined as follows; obesity, BMI ≥30 kg/m^2; over weight, 29>BMI≥25 kg/m^2; noraml weight, BMI<25 kg/m^2.

Table 3 Multiple linear regression analysis for insulin resistance and arterial properties (n=1,339)

|	Carotid IMT		PWV		HOMA-IR	
	β	p	β	p	β	p
Age (years)	0.380	<0.001	0.340	<0.001	-0.023	0.335
Sex (male)	0.015	0.584	0.051	0.010	-0.003	0.915
Body mass index (kg/m²)	0.090	0.002	-0.138	<0.001	0.378	<0.001
Antihypertensive medication	0.036	0.152	0.081	<0.001	0.029	0.221
Antihyperglycemic medication	0.105	<0.001	0.043	0.024	0.100	<0.001
HOMA-IR (log-transformed)	-0.035	0.227	0.055	0.016		
Triglyceride (mg/dl)	-0.041	0.132	0.067	0.002	0.175	<0.001
HDL cholesterol (mg/dl)	-0.084	0.003	-0.025	0.265	-0.102	<0.001
Preprandial HR (beats/min)	-0.080	0.001	0.208	<0.001	0.151	<0.001
Postprandial changes in HR (beats/min)	0.012	0.635	0.039	0.043	-0.031	0.182
Preprandial SBP (mmHg)	0.198	<0.001	0.492	<0.001	0.143	<0.001
Postprandial changes in SBP (mmHg)	0.086	0.001	0.170	<0.001	0.093	<0.001

FIGURE 1
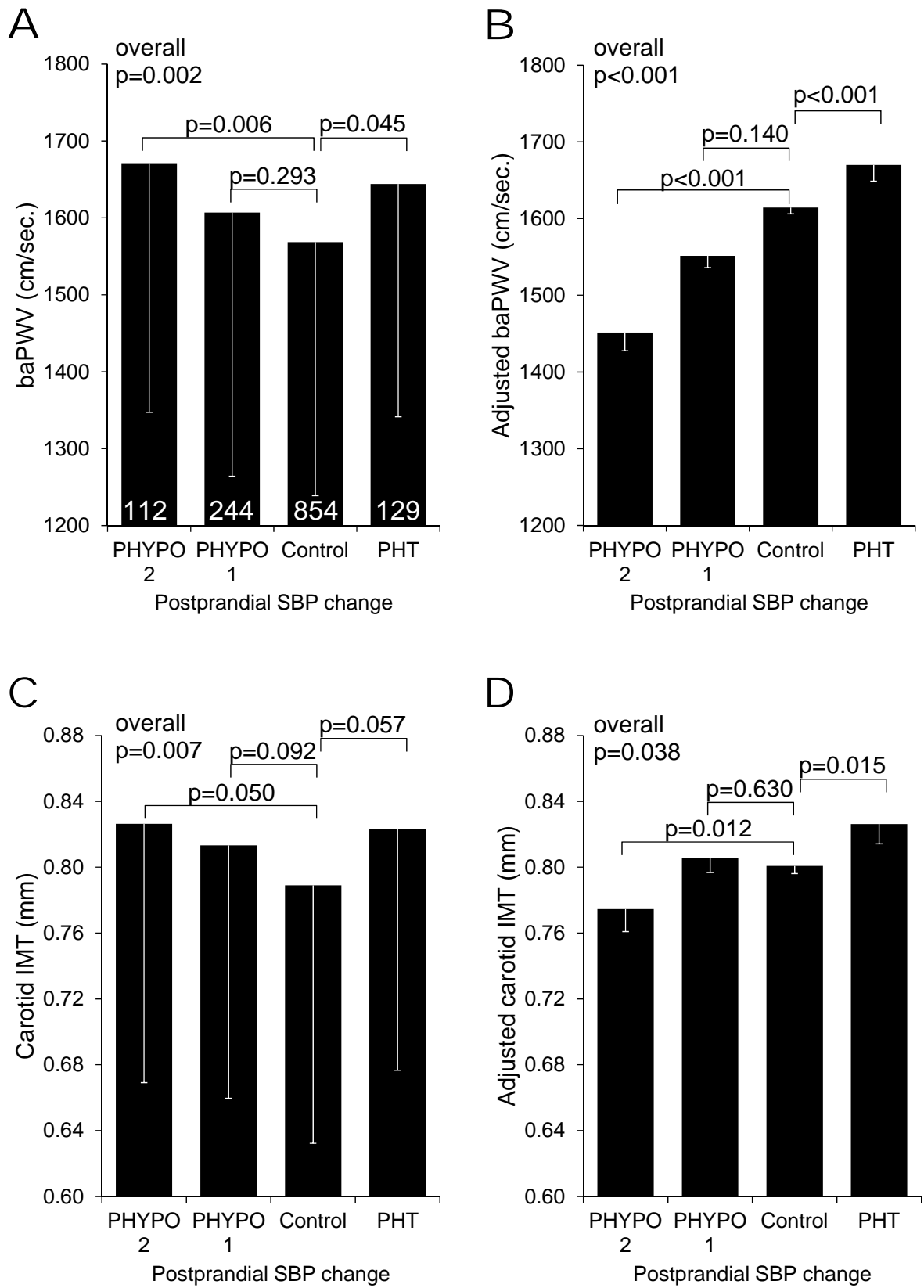
FIGURE 2
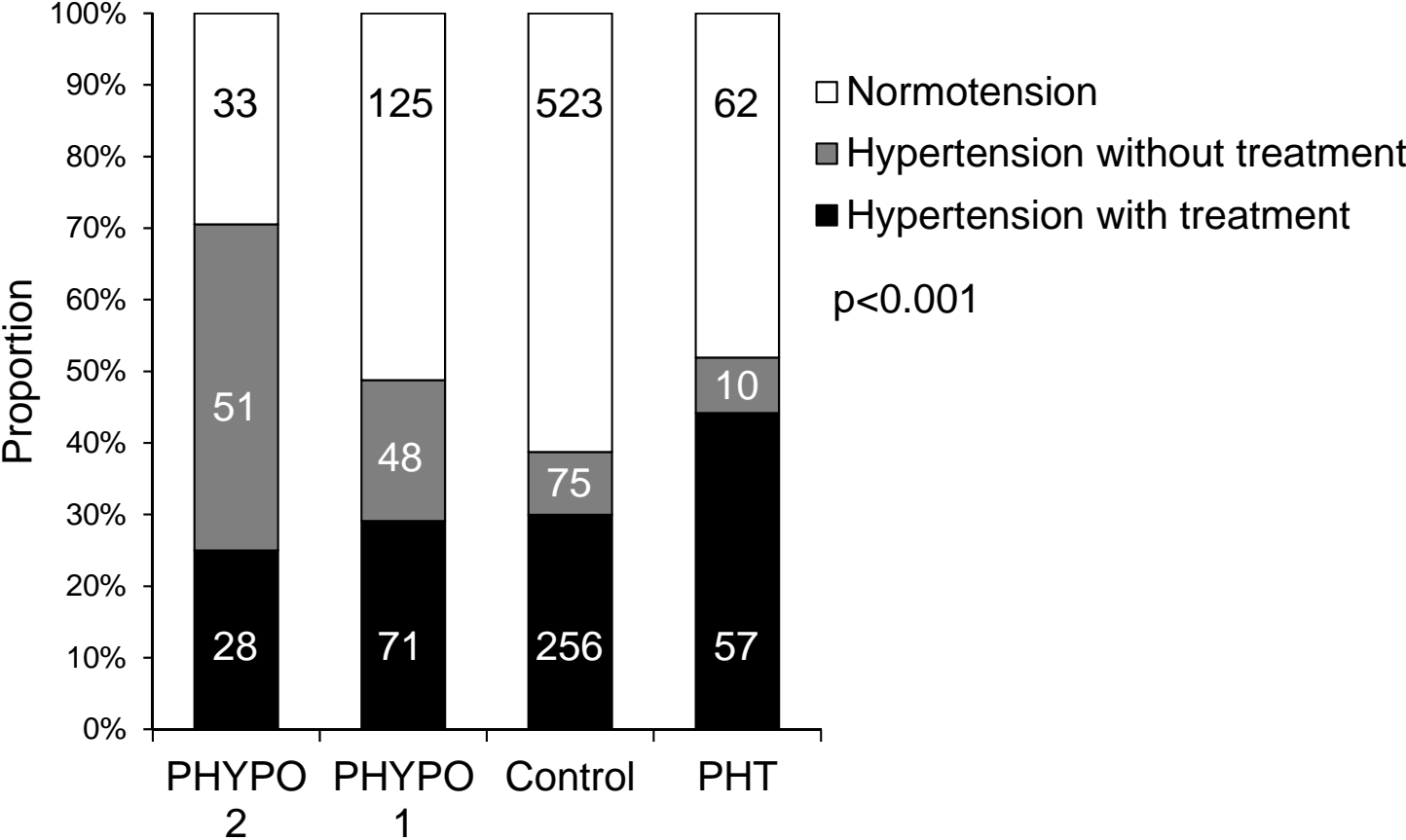
ONLINE SUPPLEMENT

Postprandial hypertension,
an overlooked risk marker for arteriosclerosis

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SUPPLEMENTAL FIGURE 1

Radial pressure wave

Radial Augmentation index (%)
= (PP2 / PP1) x 100
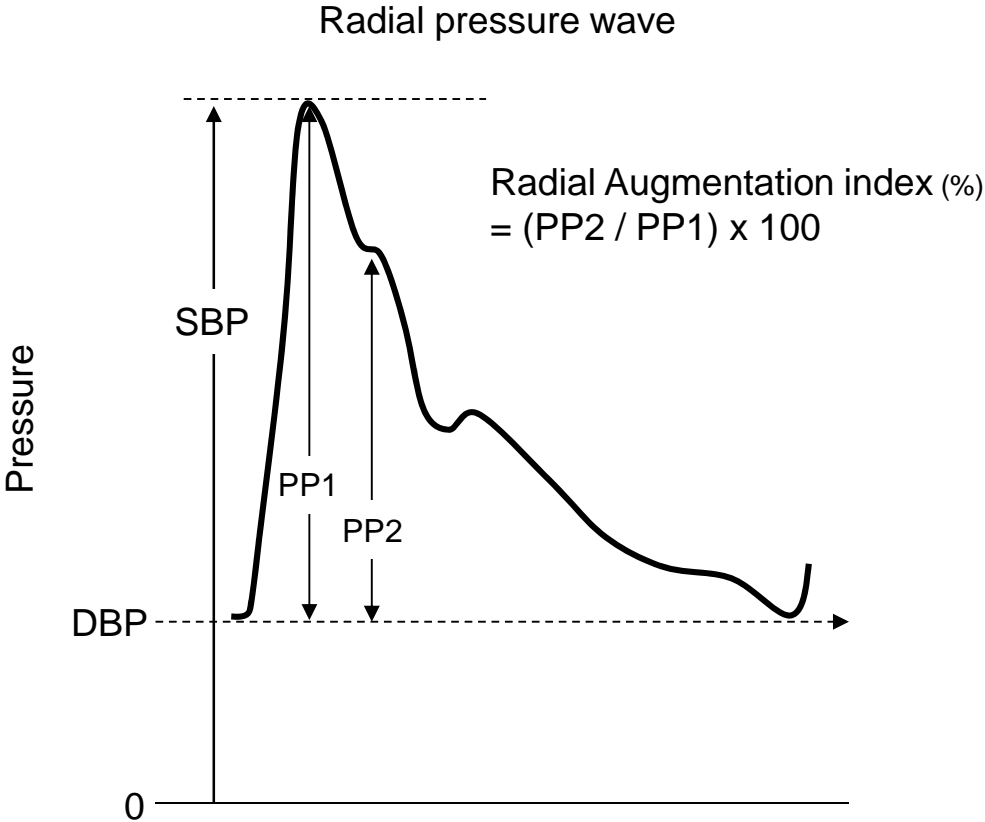
Supplemental Figure 1 Tracing the radial pressure waveform
The first and late systolic peaks of the radial pressure waveform were identified using the
fourth derivative wave as the second and third zero crossing points, respectively.

SUPPLEMENTAL FIGURE 2
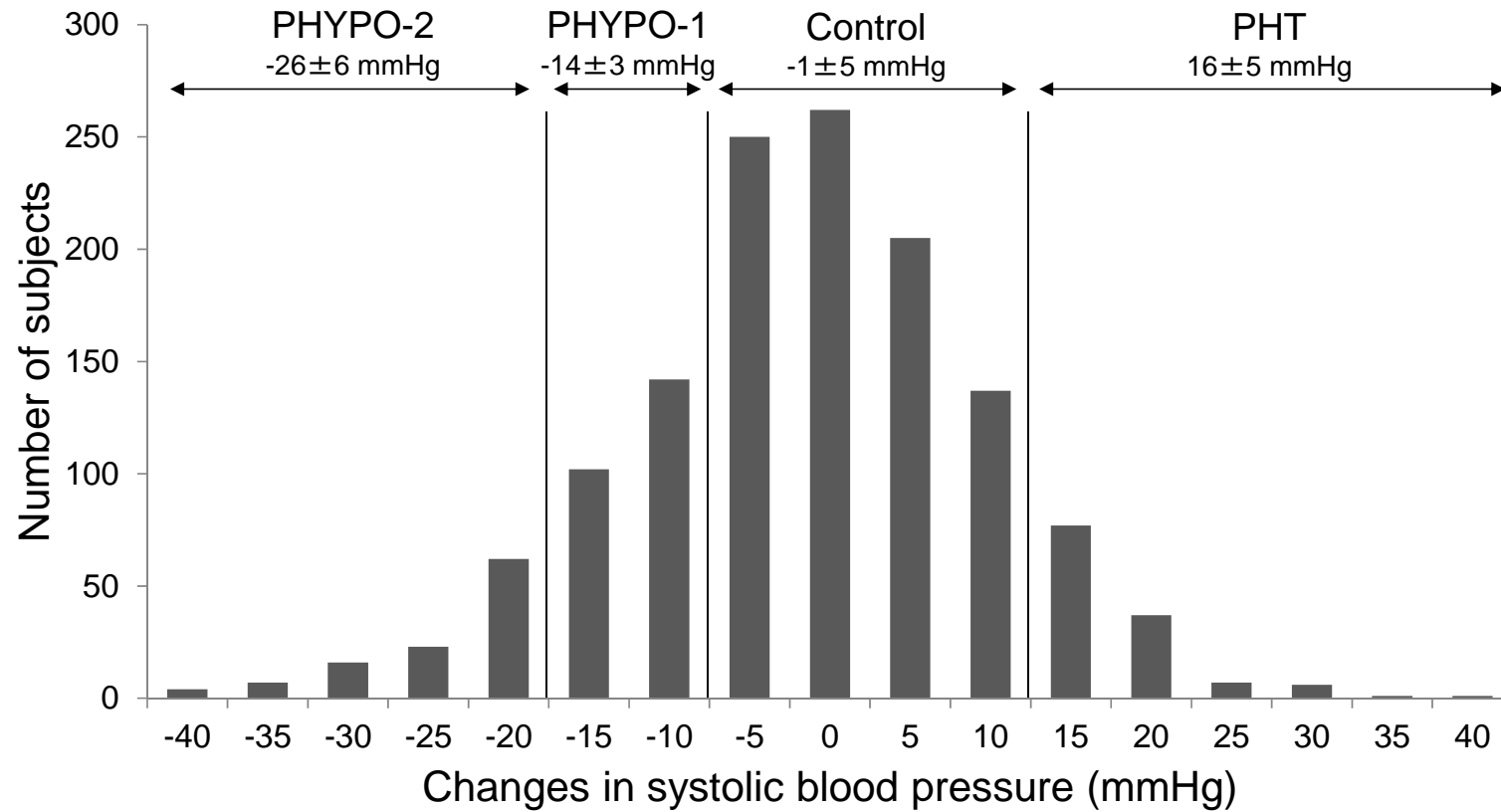
**Supplemental Figure 2 Histogram of the postprandial changes in systolic blood pressure**

Subjects were classified into four groups according to postprandial changes in systolic blood pressure, namely postprandial hypotension-2 (PHYPO-2: ΔSBP$\leq$-20 mmHg), PHYPO-1 (-20<ΔSBP$\leq$-10 mmHg), Control (-10<ΔSBP$\leq$10 mmHg), and postprandial hypertension (PHT: ΔSBP >10 mmHg).

SUPPLEMENTAL FIGURE 3
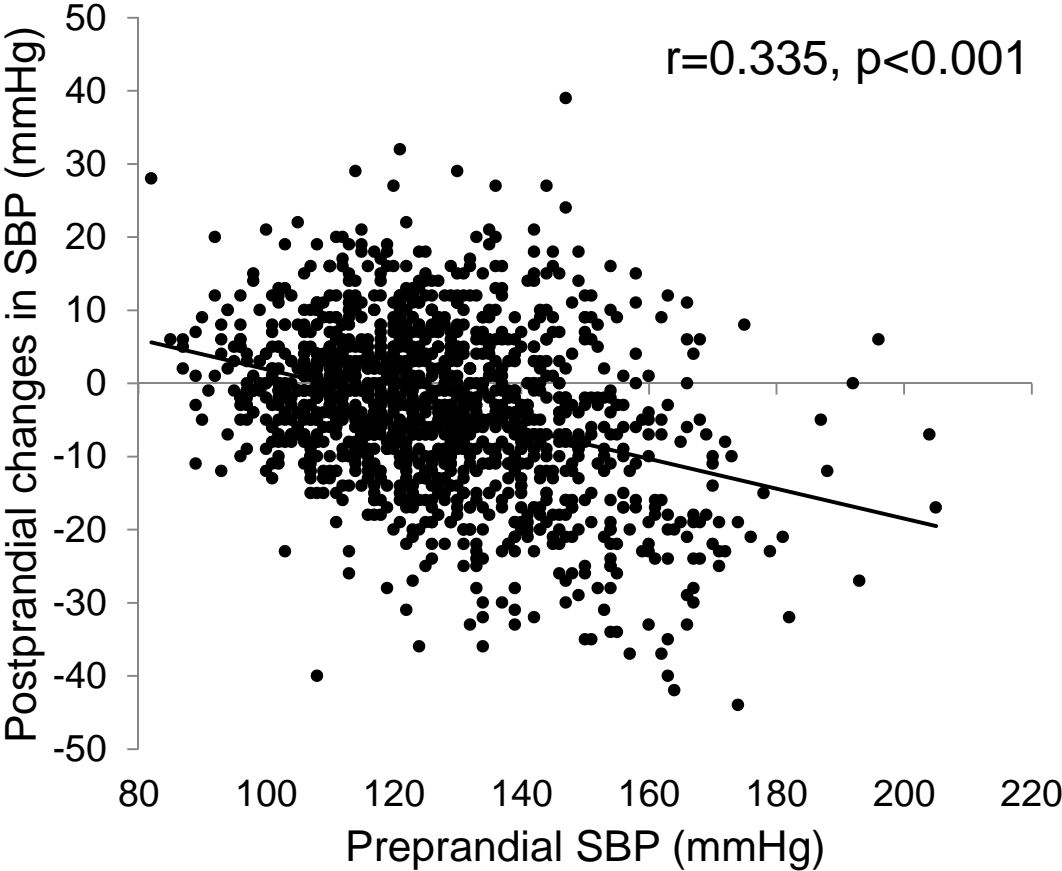
Supplemental Figure 3 Association between preprandial SBP and postprandial SBP change

SUPPLEMENTAL FIGURE 4
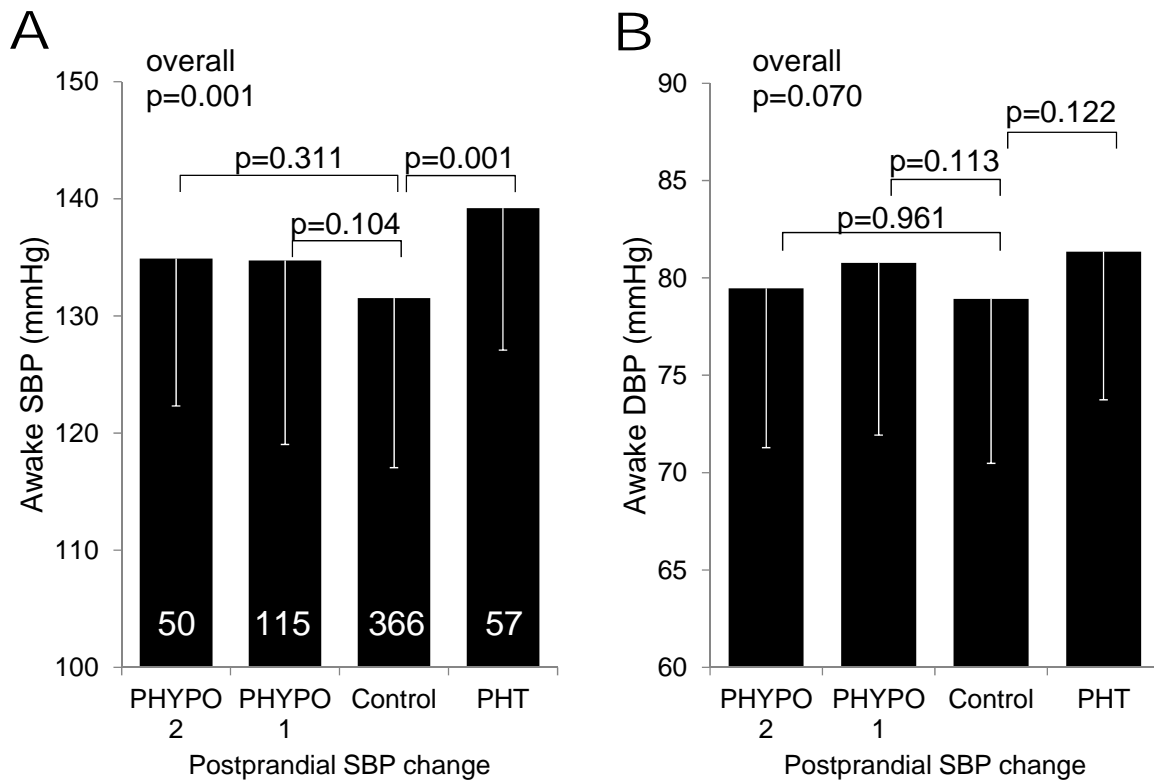
Supplemental Figure 5 Postprandial changes in SBP and ambulatory measured awake BP

Ambulatory BP was monitored using a cuff-oscillometric device (TM-2431, A&D Co. Inc., Tokyo, Japan), a fully automatic device which was pre-set to measure BP and heart rate every 15 min during the day (7 AM to 10 PM) and every 30 min at night. Number of subjects in each group is shown in the column. Statistical significance was assessed by analysis of variance (ANOVA). Post-hoc analysis was performed by the Dunnet's test.