Original Article

Orthostatic Systolic Hypotension and the Reflection Pressure Wave

Yasuharu TABARA, Jun NAKURA*, Ikuko KONDO, Tetsuro MIKI*, and Katsuhiko KOHARA*

Orthostatic hypotension (OH) is a potent predictor of cardiovascular frailty. Although OH is determined by changes in brachial blood pressure (BP), it has been reported that there are significant differences between central BP and peripheral BP. The prevalence of OH has been reported to be higher in subjects with isolated systolic hypertension. Since an early returning of the reflection pressure wave due to advanced arterial stiffness is one of the underlying mechanisms of systolic hypertension, a significant association between alterations of the reflection pressure wave and OH has been hypothesized. To explore this hypothesis, the orthostatic changes in carotid BP and arterial waveform were evaluated. The study subjects were 155 community residents (69±7 years old). Carotid and brachial BP were measured simultaneously in the supine position and 1 min after standing using a cuff-oscillometric and tonometric method. The carotid augmentation index (AIx) was obtained from the pressure waveform. The orthostatic decline of BP was more prominent in the carotid artery than the brachial artery. Nine subjects were diagnosed with orthostatic systolic hypotension (OSH) from brachial BP, while 21 subjects were diagnosed from carotid BP ($p<0.001$). The orthostatic change in carotid systolic BP was significantly associated with that in carotid AIx ($r=0.361$, $p<0.001$). The decline of the reflection component of carotid pulse pressure (−4.0±8.4 mmHg) was more prominent than that of the incident component (−1.2±9.9 mmHg, $p=0.002$). These results indicate that evaluation of brachial BP may not represent the orthostatic changes in central BP. Alteration of the reflection pressure wave could be one of the underlying mechanisms of OSH in the central artery. (*Hypertens Res* 2005; 28: 537–543)

***Key Words*: orthostatic hypotension, reflection pressure wave, augmentation index**

Introduction

Orthostatic hypotension (OH) is a commonly observed phenomenon in the general elderly population (*1–9*). OH is defined as a more than a 20 mmHg reduction in systolic blood pressure (SBP) and/or more than 10 mmHg reduction in diastolic blood pressure (DBP) during a period of 3 min after standing (*10*). Although OH is known to be one of the underlying causes of falls (*1*, *2*), it has also been shown to be an independent risk factor for cognitive dysfunction (*3*, *4*), cardiovascular disease, including stroke (*5*, *6*) and silent cerebral infarction (*7*), and mortality (*8*).

A growing body of evidence shows that the regulation of central blood pressure (BP), such as that in the aorta or carotid artery, is significantly different from that of peripheral BP, such as in the brachial artery (*11–14*). A change in brachial BP does not accurately reflect that in central BP in several conditions, such as smoking (*12*), caffeine intake (*13*) and alcohol intake (*14*). Recently, it has also been reported that squatting is associated with a larger change in aortic BP than in brachial BP (*15*). Based on these observations, it is conceivable that the orthostatic change in brachial BP does not accurately reflect that in central BP.

From the Department of Medical Genetics and *Department of Geriatric Medicine, Ehime University School of Medicine, Toon, Japan.

Address for Reprints: Katsuhiko Kohara, M.D., Ph.D., Department of Geriatric Medicine, Ehime University School of Medicine, Toon 791–0295, Japan. E-mail: koharak@m.ehime-u.ac.jp

Received July 5, 2004; Accepted in revised form May 2, 2005.

In central arteries, including the carotid artery, the pressure waveform consists of two components, the forward or incident component, and the backward or reflection component (*11*, *16*). Early return of the backward reflected pressure wave due to advanced atherosclerosis would result in augmentation of central SBP, which is one of the underlying mechanisms of systolic hypertension (*17*). Since the prevalence of OH has been reported to be higher in subjects with isolated systolic hypertension (*18*), OH may be associated with an orthostatic alteration of the reflection component of central BP.

Based on this background, we hypothesized that 1) the orthostatic change in brachial BP does not accurately reflect that in carotid BP, and 2) standing is associated with an alteration of the reflection of the pressure wave, which precipitates OH in the central arteries. To evaluate these hypotheses, the orthostatic change in carotid BP was measured using a tonometric method in community-dwelling elderly subjects free from any cardiovascular complications and medications. The arterial pressure waveform in the carotid artery was evaluated before and after standing, to examine which component of the pressure waveform is more affected in response to standing.

Methods

Study Subjects

The study subjects were participants in the cardiovascular examination of the Shimanami Health Promoting Program study (J-SHIPP) to investigate factors relating to cardiovascular disease, dementia, and death (*19*). One hundred and fifty-five subjects, aged 50 years or older with no known history or symptoms of cardiovascular disease such as stroke, transient ischemic attack, myocardial infarction, angina, congestive heart failure, or peripheral vascular disease, were enrolled in this study (mean age 68.6±6.8 years; 37 males and 118 females). They were also free from any medications. Informed consent to the procedure was obtained from each subject. All procedures were approved by the ethical committee of Ehime University School of Medicine.

Measurement of Carotid and Brachial Arterial Pressure

Brachial SBP and carotid SBP were measured using a volume-plethysmographic apparatus (form PWV/ABI; Colin Co., Ltd., Komaki, Japan). The subjects were examined in the supine position, with electrocardiogram electrodes placed on both wrists, a microphone for detecting heart sounds placed on the left sternal edge, and a brachial cuff wrapped around a plethysmographic sensor that determines the volume pulse waveform and an oscillometric pressure sensor that measures BP. Pulse volume waveforms for the brachium were recorded for 10 s using a semiconductor pressure sensor with automatic gain analysis and quality adjustment. The components over 5 Hz were stored using a pass-filter, and the wave characteristic points were automatically determined (*20*).

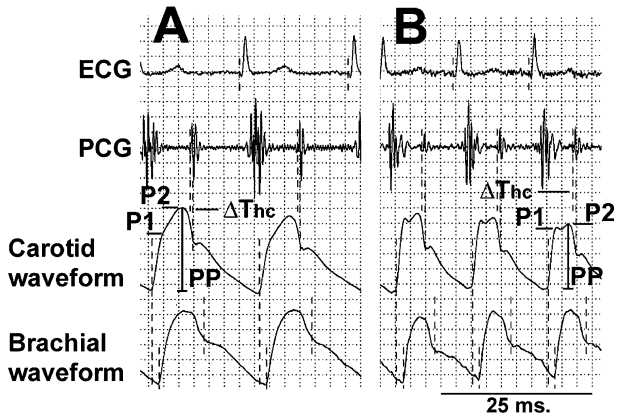

Fig. 1. *Representative tracings of orthostatic changes in brachial and carotid arterial waveforms. Two cardiograms and two waveforms, one for the carotid and one for the brachial arterial waveform, were recorded simultaneously. A shows the waveforms observed in the supine position, and B those after standing up. The dotted line indicates the characteristic points of each waveform and cardiogram. Carotid pressure waveform was analyzed according to the definition of Murgo* et al. *(*16*), and the augmentation index (%) was obtained using the equation: (P2−P1)×100/PP. In this example, the augmentation index of the carotid arterial waveform was reduced from 29% to 1%. PCG, phonocardiogram. The vertical scale is relative.*

The common carotid arterial pressure waveform was also simultaneously recorded noninvasively using a multi-element tonometric sensor (Fig. 1). The multi-element tonometry sensor consists of 15 sensitive micro-sensors within a width of 19 mm, and it automatically selects the most appropriate waveform from 15 detected pulse waveforms. The tonometry sensor for the carotid artery was fixed on the neck by means of a clip. The length of the clip-arm, angle and hold-down pressure of the sensor head were adjusted for each subject for optimal pressure wave detection. The accuracy and reproducibility of the apparatus has been reported elsewhere (*21*).

The carotid pressure wave was recorded by calibrating the brachial pressure wave, assuming that the mean BP (MBP) was the same at both sites (*22*). For this purpose, the MBP of the carotid pressure wave was computed and set equal to the brachial MBP in the corresponding heart beat. The carotid pressure amplitude was then computed from the DBP and the position of the MBP in the carotid pressure wave. Carotid SBP was calculated proportionally at the peak of the carotid arterial waveform. Invasive validation and reproducibility of measurements have been published in detail previously (*22*). The brachial SBP and carotid SBP were averaged for a series of waves over a 10-s period. Orthostatic systolic hypotension (OSH) was defined as a more than 20 mmHg decline in SBP after standing (*10*).

Table 1. Orthostatic Change in Blood Pressure in Total Population

	Supine	Standing	*p*
Brachial SBP (mmHg)	129±19	131±20	0.048
Carotid SBP (mmHg)	124±22	123±23	0.588
Carotid PP (mmHg)	46±15	41±17	<0.001
Incident component (mmHg)	31±10	30±12	0.143
Reflection component (mmHg)	16±10	12±9	<0.001
MBP (mmHg)	102±15	105±15	<0.001
DBP (mmHg)	78±11	82±11	<0.001
Heat rate (beats/min)	69±11	80±12	<0.001
Augmentation index (%)	31±16	25±18	<0.001

Values are mean±SD. SBP, systolic blood pressure; PP, pulse pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.

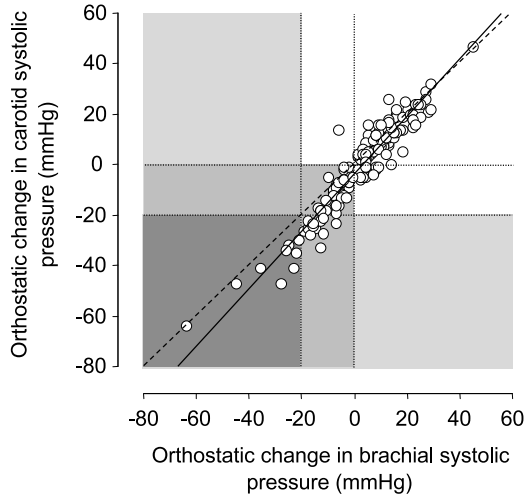

Fig. 2. *Correlation between orthostatic changes in carotid blood pressure and brachial blood pressure. The solid line is the regression line, and the dotted line is the identity line between the two variables.*

Carotid Augmentation Index (AIx)

Carotid BP at the inflection and peak of the waveform, and the time intervals of the first and second systolic peaks were obtained. The AIx was calculated as the ratio of the augmented pressure to the pulse pressure (PP) (*11*, *16*) (Fig. 1). The carotid PP was divided into two components, the backward reflection component of PP (carotid PP × AIx) and the incident component of PP (carotid PP − reflection component). The time interval between the dicrotic notch of the carotid waveform and the second heart sound of the phonocardiogram was defined as the time interval between the carotid artery and heart (ΔT_{hc}). Figure 1 shows actual tracings of the carotid and brachial pressure waveform, and the determination of AIx.

Orthostatic Changes in BP

After obtaining basal parameters in the supine position for more than 10 min, the subject was asked to stand. A brachial cuff placed around the right brachial arm was kept at the level of the heart. One minute after standing, measurements of all parameters were repeated while the subject was in the standing position. The carotid pressure wave was re-calibrated by the brachial pressure wave. Orthostatic changes in brachial SBP (Δbrachial SBP), carotid SBP (Δcarotid SBP) and AIx (ΔAIx) were obtained (Fig. 1). The percentage of orthostatic changes in the two components of carotid PP was also obtained. The percentage of orthostatic change in the reflection component of carotid PP was defined as −100% in the case that carotid AIx changed from positive to negative after standing.

Statistical Analysis

All values are expressed as the mean±SD unless otherwise specified. All analyses were performed using the SPSS software package (SPSS Inc., Chicago, USA). A probability value of less than 0.05 was considered statistically significant.

Results

Changes in brachial and carotid BP and heart rate (HR) in response to standing are summarized in Table 1. The MBP and DBP, as well as HR, were significantly increased after standing up. No significant changes were observed in carotid SBP. However, in a separate analysis, the reflection components of carotid PP showed a significant reduction, resulting in a decreased carotid PP.

Figure 2 depicts the relationship between Δbrachial SBP and Δcarotid SBP. Among all subjects, 9 (5.8%) were diagnosed as having OSH based on the change in brachial SBP, while 21 (13.5%) were diagnosed as having OSH when evaluated from the carotid SBP. The prevalence was significantly different between the two measurements ($\chi^2=61.0$, $p<0.001$). In the 9 OSH patients determined by brachial BP,

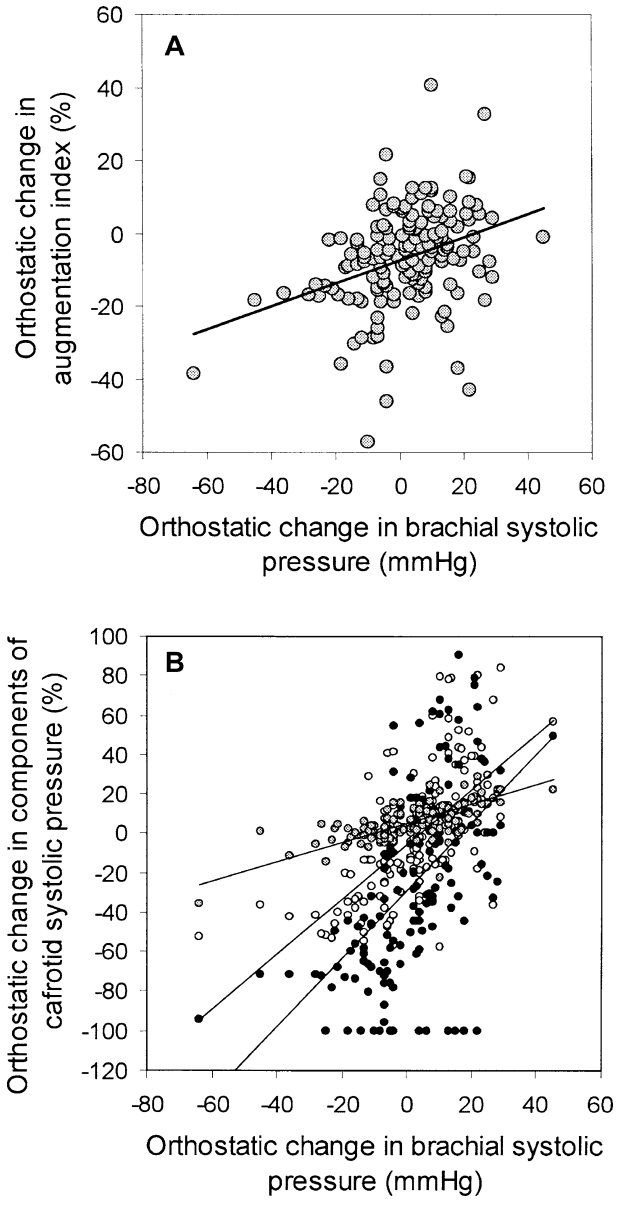

Fig. 3. *Orthostatic changes in the augmentation index and the three components of carotid pressure. A: Orthostatic change in the augmentation index (*r*=0.345,* p*<0.001). B: Orthostatic changes in the three components of carotid systolic pressure. Open circles: the incident component of pulse pressure (*r*=0.650,* p*<0.001); closed circles: the reflection component of pulse pressure (*r*=0.548,* p*<0.001); gray-circles: diastolic pressure (*r*=0.618,* p*<0.001). The analysis of co-variance indicated that the three regression lines were markedly different (*F*{3,455}=14.9,* p*<0.0001).*

the mean orthostatic change in carotid SBP was −41±11 mmHg, while that in brachial SBP was −32±14 mmHg (p=0.004). In the 12 OSH subjects classified by carotid BP but not by brachial BP, the mean orthostatic change in carotid SBP was −25±3 mmHg, while that in brachial SBP was −15±3 mmHg (p<0.001).

To evaluate the predisposing factors for brachial and carotid OSH, stepwise regression analysis was performed with the following parameters: age, sex, body height, and basal brachial SBP, HR, and AIx. Carotid OSH was significantly associated with AIx (β=0.19, p=0.015) in addition to basal brachial SBP (β=0.27, p<0.001) and age (β=0.18, p=0.020), while brachial OSH was only associated with basal brachial SBP (β=0.25, p=0.002) and age (β=0.20 p=0.012).

The significant association between Δbrachial SBP and ΔAIx is depicted in Fig. 3. Orthostatic changes in the three components of carotid SBP, *i.e.*, DBP and the incident and reflection component of PP, are also illustrated. The orthostatic reduction in the three components of carotid SBP were significantly associated with Δbrachial SBP. Although both the incident and the reflection components of carotid PP were markedly reduced, the decline of the reflection component (−4.0±8.4 mmHg) was much greater than that of the incident component (−1.2±9.9 mmHg, p=0.002). Representative tracings of the carotid arterial pressure waveform in one subject with OSH are shown in Fig. 1.

To assess the mechanism underlying the change in AIx in response to standing up, the association between orthostatic change in AIx and that in the arrival time of the reflection pressure wave (T_r) was evaluated. The results showed that orthostatic change in AIx was significantly related with that in T_r (r=0.21, p=0.010).

The hemodynamic characteristics of the OSH subjects are revealed in Table 2. The OSH subjects, assessed by the Δcarotid SBP as well as the Δbrachial SBP, showed significantly higher basal SBP, MBP and AIx compared with orthostatic normotension (ON) subjects. The ΔAIx was also significantly higher in the OSH group, which was partly responsible for the severe orthostatic decline of SBP. On the other hand, in the OSH subjects, the decline of MBP in response to standing up was significantly less than that of SBP. The Δcarotid SBP (−22±8%) was significantly higher than the ΔMBP (−12±8%, p<0.001). The Δbrachial SBP (−22±10%) was also significantly higher than the ΔMBP (−17±11%, p=0.002).

Discussion

In the present study we observed that carotid OSH was associated with a higher basal carotid AIx, in addition to advanced age and high brachial SBP. AIx has been associated with cardiovascular risk (*23*), and has recently been shown to independently predict coronary artery disease (*24*). Furthermore, AIx has been shown to be associated with mortality in the elderly (*7*). A background of high AIx may be responsible for the higher morbidity and mortality in OSH subjects.

The prevalence of isolated systolic hypertension, showing basal brachial SBP ≥140 mmHg and DBP <90 mmHg, was also higher in subjects with OSH (7 of 21 subjects) than in the ON group (13 of 134, p=0.008). An early returning of the

Table 2. Hemodynamic Characteristics of Orthostatic Systolic Hypotension Subjects

	Orthostatic carotid SBP change			Orthostatic brachial SBP change		
	OSH (21)	ON (134)	*p*	OSH (9)	ON (146)	*p*
Basal						
Carotid SBP (mmHg)	145±21	121±20	<0.001	151±26	123±21	<0.001
Brachial SBP (mmHg)	146±19	126±18	<0.001	151±23	127±18	<0.001
MBP (mmHg)	116±15	100±14	<0.001	120±18	101±14	<0.001
DBP (mmHg)	86±11	76±11	<0.001	87±14	77±11	0.010
Augmentation index (%)	41±15	30±15	0.001	44±12	30±15	0.012
Heart rate (beat/min)	68±11	69±11	0.761	67±11	69±11	0.594
Orthostatic changes in						
Carotid SBP (mmHg)	−32±11	4±13	<0.001	−41±11	2±15	<0.001
Brachial SBP (mmHg)	−22±13	6±11	<0.001	−32±14	5±12	<0.001
MBP (mmHg)	−14±9	6±9	<0.001	−19±11	5±10	<0.001
DBP (mmHg)	−3±7	6±6	<0.001	−5±10	5±7	<0.001
Augmentation index (%)	−17±10	−5±14	<0.001	−18±10	−6±14	0.008
Heart rate (beat/min)	15±6	10±6	0.004	16±7	11±6	0.010

Values are mean±SD. OSH, orthostatic systolic hypotension defined as more than 20 mmHg decline in SBP; ON, orthostatic normotension (except for OSH subjects); SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure.

reflection pressure wave caused by an enhanced arterial stiffness was thought to be a principal reason for the enhanced AIx and isolated systolic hypertension. Recently, a significant association between carotid-brachial pulse wave velocity (PWV) and orthostatic BP response was reported in elderly subjects (*25*). In a previous study, we also demonstrated a relationship between orthostatic BP decline and carotid intima-media thickening (*26*). These reports together with the present findings indicate that enhanced arterial stiffness plays a significant role in the orthostatic BP dysregulation.

Although the present study was not designed for detailed elucidation of the mechanism responsible for the decline in AIx after standing, there seem to be several possible mechanisms. The magnitude of AIx is dependent on the distance from the reflection site, the velocity of wave conduction, as well as the reflectance (the reflection efficacy) (*27*). In the present study, we observed that orthostatic change in carotid AIx was significantly associated with that in T_r. Both the distance to the reflection point and the wave velocity influenced the timing of the return of the reflection wave. The distance to the reflection point is technically considered to be the body height. It has been shown that short stature is associated with high AIx (*28*). Since change in arterial impedance could influence the reflection point, it is conceivable that postural change from a supine to a standing position could change the reflection point through the change in impedance (*11*). It is also conceivable that OH itself could reduce AIx by reducing the wave velocity, since it is well known that PWV is highly dependent on BP. On the other hand, the changes in HR should also be considered as a confounding factor for the pressure waveform. It has been well demonstrated that an increase in HR will decrease the absolute duration of systole, effectively shifting the reflected wave into diastole, and thereby reducing AIx (*29*). The sympathetically increased HR in response to orthostatic stimuli could be another underlying mechanism of the orthostatic decline in AIx.

Neuronal dysregulation of BP plays a pivotal role in OH. In patients with autonomic dysfunction, OH results from an impaired capacity to increase vascular resistance during standing (*30*). The neuronal dysfunction leads to increased downward pooling of venous blood and a consequent reduction in stroke volume and cardiac output that exaggerates the orthostatic fall in BP (*30*). On the other hand, the enhanced arterial stiffness attenuates the baroreceptor response, since carotid and aortic baroreceptors locate in the arterial wall and are triggered by stretch. It has been reported that there is an inverse relationship between carotid distensibility and baroreceptor function (*31*).

Since none of the subjects had any orthostatic symptoms during examination, we should be cautious in extending our findings to subjects with orthostatic symptoms. However, it should be emphasized from our study that a lack of a significant orthostatic change in brachial BP does not eliminate the possibility of OSH in subjects with symptoms like light-headedness, since it could relate to cerebral hypoperfusion. In the present study, all subjects were free from any medications, including antihypertensive drugs. Since there is accumulating evidence that antihypertensive drugs have class-specific effects on central BP independent of the effect on brachial BP (*32*), it is also conceivable that the orthostatic change in carotid BP could be greatly exaggerated in subjects on antihypertensive medication. Further study is needed to clarify this very important issue.

There were several study limitations. First, we were not

able to consider the hydrostatic effect when evaluating the orthostatic BP response. Since a decreased hydrostatic pressure induces a baroreceptor unloading in addition to the effect of decreased cardiac preload, excessive baroreceptor-evoked sympathoexcitation might have occurred in the study procedure. However, in the OSH subjects, the orthostatic change in HR was not larger than that of the ON group. The impaired baroreceptor function might be involved in the destabilization of BP after the postural change. Secondly, we defined the carotid OSH as a decline in carotid SBP ≥20 mmHg. However, the application of the criteria based on the changes in brachial SBP to the carotid SBP was not validated. Thirdly, we evaluated the orthostatic changes in BP and AIx by single measurement at 1 min after standing up. It has been reported that the measurement of SBP after 1 min of upright posture was twice as sensitive as a single measurement at 3 min in elderly subjects (*33*). However, the time-dependence of the alteration of orthostatic BP has been well documented (*34*). We have also reported that the time elapsed after standing up could affect the prevalence of OH (*35*). Sequential measurements could thus provide additional information that might help to clarify the association between altered AIx and OSH.

In summary, the findings of the present study indicate that evaluation of OSH from brachial BP may underestimate the prevalence of OSH as well as the magnitude of BP change, especially in elderly subjects with higher carotid AIx and individuals with high SBP. OSH was associated with a significant reduction of the reflection component of carotid PP in addition to a significant decrease in the incident component. Although further study is necessary, intervention to manipulate the reflection wave could be a therapeutic option in OSH.

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