Original Article

Acute Decrease of Cardio-Ankle Vascular Index with the Administration of Beraprost Sodium

Mao Takahashi¹, Tomoaki Shiba², Keiichi Hirano¹, Takashi Hitsumoto¹ and Kohji Shirai¹

¹Department of Internal Medicine, Sakura Hospital, Medical Center, Toho University Chiba, Japan
²Department of Ophthalmology, Sakura Hospital, Medical Center, Toho University Chiba, Japan

Aim: A novel arterial stiffness index, the cardio-ankle vascular index (CAVI), has been proposed. To clarify the properties of CAVI, the effects of beraprost sodium (BPS), a prostaglandin (PG) I₂ analogue, which has a potent vasodilating effect, on CAVI were studied and comparing with brachial-ankle pulse wave velocity (baPWV) in healthy volunteers.

Methods: Male volunteers (n = 18, 46.3 ± 4.2 yr) were enrolled in this study and administered BPS (40 μg). CAVI and baPWV were measured every hour for 4 hours.

Results: When BPS was administered to 18 healthy volunteers, systolic blood pressure and diastolic blood pressure fluctuated slightly, but the means did not change. CAVI significantly decreased in the 1st hour from 8.3 ± 0.34 (mean ± SE) to 7.9 ± 0.34 (p < 0.05) and this decrease persisted for 3 hours, whereas baPWV did not significantly change. ΔbaPWV each time was significantly correlated with both Δsystolic blood pressure and Δdiastolic blood pressure, but ΔCAVI did not correlate with either Δsystolic blood pressure (r = −0.12, p = 0.38) or Δdiastolic blood pressure (r = −0.22, p = 0.10).

Conclusions: Beraprost sodium did not decrease blood pressure, but decreased CAVI, whereas baPWV did not change. These results indicate that CAVI partly reflected the contraction of arterial smooth muscle cells.


Key words: Vasodilatory effects, Beraprost sodium, Stable prostacyclin analogue, Cardio-ankle vascular stiffness index, Arterial stiffness parameter

Introduction

Arteriosclerosis is a major contributor to cardio- and cerebrovascular disease accounting for most of its mortality and morbidity¹, ²). Arterial stiffness is considered to reflect arteriosclerosis and can be measured non-invasively. Several parameters reflecting arterial stiffness have been proposed. Pulse wave velocity (PWV) has been proposed and is used currently³-⁵), and many valuable data have been reported⁶-⁹); however, a problem of PWV in clinical use is that PWV itself is an indirect method reflecting arterial wall stiffness at the measuring time¹¹, ¹²).

Recently, the cardio-ankle vascular index (CAVI) was proposed, which essentially represents the stiffness parameter of the aorta, femoral artery and tibial artery. It is theoretically independent of blood pressure, because CAVI is measured from stiffness parameter β, which was proposed by Hayashi et al.¹³), and which is based on the arterial pressure variance required for a change in the vascular diameter. An increase in CAVI suggests a high prevalence of cardiovascular disease¹⁴, ¹⁵) and microvascular complication¹⁶-¹⁸). Contributing factors, such as collagen, elastin, and proteoglycans for arterial stiffness are assumed¹⁹, ²⁰). The arterial wall also contains smooth muscle cell layers, but the involve-
ment of smooth muscle cells in arterial stiffness has not yet been clarified.

Thus, in order to prove the value of CAVI is reflecting smooth muscle cell contraction, we examined the relationship between CAVI and the vasodilation of peripheral vessels by a vasodilatory agent. Beraprost sodium (BPS), a prostaglandin I₂ (PGI₂) analog, was developed as a potent vasodilator and has been used for the treatment of chronic occlusive disease since 1992, and pulmonary hypertension since 199921. BPS improves microcirculation, is a potent vasodilator and inhibitor of platelet activation, and has few effects on blood pressure. BPS is supposed to improve arterial stiffness independent of blood pressure at the measuring time22, 23. So CAVI would be decreased after BPS administration. As stated above, baPWV is known to depend on blood pressure at the measuring time. To confirm the independence of CAVI from blood pressure at the measuring time, CAVI and baPWV were simultaneously measured during the administration of BPS as a PGI₂ analogue, every hour for 4 hours to 18 male volunteers. In addition, blood pressure dependence was also compared between CAVI and baPWV.

**Subjects and Methods**

**Subjects**

The subjects were 18 male volunteers, ranging in age from 32 to 57 years old. None of them smoked at the time of administration of BPS. They were administrated 40 μg BPS, and CAVI and baPWV were measured in a supine position after a 10- minute rest each time. During the interval between measuring times, they rested in a sitting position. Informed consent was obtained from all participants, and the study was approved by the Research Ethics Board of Sakura Hospital, Toho University.

**Measuring CAVI and baPWV**

At the measuring time, volunteers rested for 10 minutes in a supine position. The precise methods were described in the previous report11. Briefly, to detect the brachial and ankle pulse waves using cuffs, the pressure of cuffs remained low, from 30 mmHg to 50 mmHg, to ensure the minimal effect of cuff pressure on hemodynamics. Blood pressure was measured after detecting the pulse. baPWV was calculated simultaneously11. All these measuring tools and the calculation system were included in VaSera (Fukuda Denshi Co. Ltd, Tokyo).

**Statistical Analysis**

Data are presented as the mean ± standard error (SE) for continuous variables. Groups were compared using repeated measures ANOVA followed by the Bonferroni test for comparison of the response curves. Relationships between ΔCAVI or ΔbaPWV, and Δsystolic blood pressure and diastolic blood pressure were analyzed by Pearson's correlation coefficient. P<0.05 was considered significant. Statistical analysis was performed using Stat View j-5.0 (SAS Institute, Cary, NC, USA).

**Results**

**Effect of Beraprost Sodium Administration on Blood Pressure, CAVI and baPWV (Fig. 1)**

BPS (40 μg) was administered to 18 volunteers. Systolic blood pressure (sBP) and diastolic blood pressure (dBP) did not change after BPS administration in the 1st, 2nd and 3rd hours (sBP: 125.2 ± 3.7 (Pre), 122.8 ± 2.4 (1st hour), 123.9 ± 3.0 (2nd hour), 126.8 ± 3.3 (3rd hour) mmHg, dBP: 79.5 ± 2.5 (Pre), 76.2 ± 2.3 (1st hour), 78.4 ± 2.0 (2nd hour), 78.6 ± 2.4 (3rd hour) mmHg). baPWV decreased slightly after administration of BPS in the 1st, 2nd and 3rd hours (baPWV: 12.0 ± 0.7 (Pre), 11.8 ± 0.6 (1st hour), 11.8 ± 0.6 (2nd hour), 11.7 ± 0.6 (3rd hour), 12.1 ± 0.7 (4nd hour) m/sec).
Correlation between Fluctuations of Blood Pressure

CAVI decreased significantly after administration of BPS in the 1st hour from 8.4 ± 0.3 to 7.8 ± 0.3 (p < 0.05) and this decrease persisted for 3 hours (CAVI: 7.9 ± 0.3 (2nd hour), 8.0 ± 0.3 (3rd hour)). In addition, CAVI returned to the baseline level after 4 hours (8.5 ± 0.3).

Correlation between Fluctuations of Blood Pressure and Difference in Arterial Stiffness Parameters

As shown in Fig. 2, A, B, C, D, the differences in arterial stiffness parameters (Δ) between before and after BPS administration in each hour were calculated as well as changes in blood pressure during drug administration, showing no significant changes with fluctuations of systolic blood pressure or diastolic blood pressure and ΔCAVI or, ΔbaPWV. There was no significant correlation between the change in ΔCAVI and Δsystolic blood pressure or Δdiastolic blood pressure (r = −0.12, p < 0.38, r = −0.22, p=0.10, respectively); however, positive correlations between the change in ΔbaPWV and systolic blood pressure or diastolic blood pressure (r = 0.35, p < 0.009, r = 0.386, p < 0.003, respectively) were observed.

Fig. 2. Correlations between ΔCAVI or ΔbaPWV and Δblood pressure during Beraprost sodium administration.

Differences in vascular parameters (Δ) between before and after Beraprost sodium administration each hour were calculated and their correlations shown.
A, B: Correlations among ΔbaPWV, Δsystolic blood pressure (A) and Δdiastolic blood pressure (B) during Beraprost sodium administration.
C, D: Correlations among ΔCAVI, Δsystolic blood pressure (C) and Δdiastolic blood pressure (D) during Beraprost sodium administration.
Discussion

This study was designed to investigate the effects of BPS, a potent vasodilator, on CAVI and baPWV. Some researchers have reported that BPS improves arterial stiffness by affecting the microcirculation and scarcely affects blood pressure\(^{22, 23}\).

In this report, we show the data for decreased CAVI after administration of beraprost sodium at a dose of 40 \(\mu g\) only as the maximum dose in the clinical setting, but administration of a half-dose of BPS (20 \(\mu g\)) did not decrease sBP, dBP, baPWV and CAVI in a small group of healthy volunteers (data not shown). When BPS (40 \(\mu g\)) was administered to 18 men, systolic blood pressure and diastolic blood pressure fluctuated slightly, and the mean did not change; however, CAVI significantly decreased in the 1st hour from 8.3 \(\pm\) 0.34 (mean \(\pm\) SE) to 7.9 \(\pm\) 0.34 \((p < 0.05)\) and this decrease persisted for 3 hours. There was no significant inverse correlation between the change in \(\Delta\)CAVI and \(\Delta\)systolic blood pressure \((r = -0.12, p = 0.38)\) or \(\Delta\)diastolic blood pressure \((r = -0.22, p = 0.10)\) during administration of BPS. This suggested that CAVI was independent of blood pressure at the measuring time and might reflect the stiffness of the artery wall itself.

The reduction effect of BPS on CAVI could be mediated by the function of endothelial cells. PGI\(_2\) is primarily generated in vascular endothelial cells and plays a crucial role in the regulation of local vascular tone\(^{24, 25}\). PGI\(_2\)-induced relaxation of smooth muscle cells is believed to be mediated by activation of the PGI\(_2\) receptor, which leads to elevation of cAMP levels in vascular smooth muscle cells\(^{26}\). Another researcher has reported that BPS increased eNOS expression both in vivo using cultured aortic endothelial cells and in vitro\(^{27}\). In our results, the decrease of CAVI by the administration of BPS can be explained by the vasodilation functions of smooth muscle cells through the biosynthesis and release of nitric oxide.

This study demonstrates different responses in the acute phase by administration of BPS on baPWV and CAVI, although both CAVI and baPWV include the stiffness not only of elastic arteries, but also of muscular arteries. A previous report has shown that baPWV did not change acutely with the administration of BPS during the 2 hours in which arterial stiffness improved\(^{21}\). Our results also showed that baPWV did not change during BPS administration in the acute phase (Fig. 1), but changed with the fluctuations of blood pressure during BPS administration. The underlying mechanism of the different response of CAVI and baPWV remained elusive in this study; however, it was reported that baPWV includes two components: blood pressure and arterial stiffness\(^{12}\). On the other hand, CAVI is independent of blood pressure\(^{11}\), so sensitivity in the acute phase for smooth muscle contraction was induced by BPS administration in a small group of middle-aged healthy subjects. Furthermore, aortic stiffness is influenced at each site from the origin of the aorta to the ankle point of the tibial artery during administration of BPS. CAVI reflects the stiffness of the whole arterial segment, composed of the aorta, femoral artery and tibial artery\(^{11}\). CAVI can be calculated from PWV at the origin of the aorta to the ankle portion of the tibial artery, and systolic and diastolic blood pressure in the upper brachial artery. This index was originally derived from stiffness parameter \(\beta\), proposed by Hayashi\(^{13}\) and Kawasaki et al. On the other hand, baPWV reflects the stiffness of the segment composed of the abdominal unknown arterial point, femoral artery and tibial artery. Hence, CAVI could be expressed as the acute influence on whole aortic vessels during administration of BPS. To confirm this hypothesis, further study of the influence of BPS on the elastic aorta, muscular aorta and resistance arterial vessels is needed.

Regarding microvascular complications, Kubozono et al. reported that chronic kidney disease (CKD) was related to CAVI in the general population\(^{16}\). Kim et al. also demonstrated that CAVI is closely related to CKD and neuropathy in type 2 diabetic mellitus\(^{18}\). The reason why CAVI showed a positive relationship with microvascular complications warrants discussion. The structure of the arterial wall is complicated. It is composed of an endothelial cell layer, intimal layer, medial layer and adventitia. These components are composed of various fibers, such as collagen and elastin, proteoglycans and smooth muscle cells\(^{28-30}\). Furthermore, muscular arteries are under the control of nerves and vasoactive hormones, such as catecholamine\(^{31}\), angiotensin\(^{32}\), and also calcium ions\(^{33}\) as vasoconstrictors, as well as nitric oxide as a vasodilator\(^{34}\). More detailed studies on the effects of various factors on CAVI are required.

In summary, arterial stiffness involves at least two factors; the amount of matrix, and the degree of smooth muscle cell contraction. Our results indicate that CAVI was affected not only by solid components such as elastin, collagen or other matrix components, but also by the degree of smooth muscle cell contraction regulated by vasodilator agents such as BPS.

Conclusion

It was shown that CAVI is decreased by BPS, a
potent vasodilator, independently of blood pressure, and could reflect the stiffness of the aorta, femoral artery and tibial artery as a whole. CAVI could reflect the stiffness of the arterial wall composed of smooth muscle tone in addition to the stiffness of the matrix component.

References

4) Paine RM: Pulse-wave velocity as an index of aging in the cardiovascular system, J Gerontol, 1948; 3; 303-305
5) Hallock P: Arterial elasticity in man in relation to age as evaluated by the pulse wave velocity method. Arch. Intern. 1934; 54: 770-798
27) Palmer RM, Ferrige AG, Moncada S: Nitric oxide release
28) Murata K, Motayama T, Kotake C: Collagen types in various layers of the human aorta and their changes with the atherosclerotic process. Atherosclerosis, 1986; 60: 251-262