Original Article

Contradictory Effects of β 1- and α 1- Adrenergic Receptor Blockers on Cardio-Ankle Vascular Stiffness Index (CAVI)

— CAVI is Independent of Blood Pressure —

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Aim: The cardio-ankle vascular stiffness index (CAVI) is a new parameter that reflects the stiffness of the aorta, femoral artery and tibial artery as a whole. One of its conspicuous features is that CAVI is independent of blood pressure at measuring time, theoretically. But, it has not been experimentally proved yet. For confirmation, pharmacological studies were performed comparing with brachial-ankle pulse wave velocity (baPWV).

Methods: Used drugs were a β 1-adrenoceptor blocker, metoprolol and an α 1- adrenoceptor blocker doxazosin. Both were administered to 12 healthy volunteer men. CAVI and baPWV were measured every one hour for 6 hours using VaSera.

Results: When metoprolol (80 mg) was administered to 12 healthy volunteer men, systolic blood pressure decreased from 131.4 ± 4.5 to 118.3 ± 4.1 mmHg (mean $\pm$ SE) ($p < 0.05$) at the 3rd hour, and diastolic blood pressure decreased from 85.3 ± 4.0 to 75.3 ± 3.0 mmHg ($p < 0.05$). baPWV decreased from 13.93 ± 0.46 to 12.46 ± 0.49 m/sec ($p < 0.05$), significantly, but CAVI did not change (8.16 ± 0.29 to 8.24 ± 0.27) ($p = 0.449$). Δ baPWV at each time was significantly correlated with both Δ systolic and Δ diastolic blood pressures, but Δ CAVI was not correlated with either Δ blood pressure. When doxazosin (4 mg) was administered to the same men, systolic blood pressure decreased from 130.2 ± 4.6 to 117.2 ± 4.8 mmHg ($p < 0.05$) at the 3rd hour. Diastolic blood pressure also decreased from 85.1 ± 4.1 to 74.2 ± 3.9 mmHg ($p < 0.05$). baPWV decreased from 13.98 ± 0.68 to 12.25 ± 0.53 m/sec ($p < 0.05$), significantly. CAVI also decreased from 8.15 ± 0.28 to 7.18 ± 0.37 ($p < 0.05$), significantly.

Conclusion: These results suggested that CAVI was not affected by blood pressure at the measuring time directly, but affected by the changes of contractility of smooth muscle cells.

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Key words; Cardio-ankle vascular stiffness index, CAVI, Arterial stiffness, α 1-Antagonist, Doxazosin, β 1-Antagonist, Metoprolol, Blood pressure

Introduction

Measuring arterial stiffness would provide valuable information about arterial wall conditions, which include sclerosis and contraction of arterial smooth muscles¹⁾. Several parameters reflecting arterial stiffness have been proposed, including pulse wave velocity (PWV)²⁻⁴⁾. The importance of measuring PWV as a marker of arteriosclerosis was pointed out^{5,6)}. In 1990,

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baPWV was proposed⁷⁾ and its utility as a predictive marker of multiple coronary artery occlusive disease was reported⁸⁾. However, it has been reported that PWV depends on blood pressure at the time of measurement⁵⁾. It is therefore difficult to know the real arterial stiffness by measuring PWV, and it is also inadequate to evaluate the effect of controlling hypertension with blood pressure-lowering agents on arterial wall condition itself. Hasegawa and coworkers⁹⁾ proposed corrected aortic PWV (cPWV), which reflects PWV from the origin of the aorta to the femoral artery. They made a monograph to correct aortic PWV for diastolic blood pressure adjusted to 80 mmHg. The utility of cPWV has been mentioned^{10, 11)}. However, this method does not reflect arterial stiffness directly and has problems detecting the pulse of the femoral artery in the inguinal area.

In 2006, a new blood pressure-independent arterial wall stiffness parameter, the cardio-ankle vascular stiffness index (CAVI), was proposed¹²⁾. The properties of CAVI^{13, 14)} and its clinical significance for diabetes mellitus¹⁵⁾, carotid arteriosclerosis, hypertension¹⁶⁾, coronary arterial disease¹⁷⁾ and renal disease^{18, 19)} were reported recently, suggesting that CAVI increased in arteriosclerotic diseases and was scarcely affected by blood pressure^{12, 15)}.

Theoretically, CAVI is independent of blood pressure at the time of measurement¹²⁾, because CAVI is essentially originated from stiffness parameter β ^{20, 21)}. But, it has not been experimentally proved yet.

To address this, we studied CAVI changes while the blood pressure was changed using two agents with different mechanisms to lower blood pressure. One is β 1-adrenergic receptor blocker. β 1-Adrenergic receptor exists in the heart muscle and enhances the contraction and the pulse of the heart^{22, 23)}. We chose metoprolol as the β 1 selective blocker²³⁾. It is supposed to decrease blood pressure by reducing heart muscle contraction, not by vasodilation. If CAVI would be dependent on blood pressure at the measuring time, CAVI would decrease when blood pressure decreased by β 1 blocker.

The other used agent was α -1 adrenergic receptor blocker. α -1 Adrenergic receptor exists in vascular smooth muscle cells and induces contraction of the artery wall and raises the blood pressure^{24, 25)}. As the α -1 selective blocker, we chose doxazosin²⁵⁾. Doxazosin inhibits the binding of norepinephrine to α -1 adrenergic receptor in vascular smooth muscle cells, resultantly relaxing vascular smooth muscle cell tone, which decreases peripheral vascular resistance, leading to a decrease in blood pressure^{24, 25)}. In this case, CAVI would be expected to decrease.

For these confirmations, both agents were administered to healthy 12 volunteer men alternatively at 7-day intervals. CAVI and baPWV were measured every hour for 6 hours, simultaneously. The correlations between the changes of CAVI or of baPWV (Δ CAVI or Δ baPWV = value before – value at each time, respectively), and blood pressure changes (Δ BP = value before – value at each time) during the administration of both agents were also studied.

Subjects and Methods

Subjects

The subjects were 12 male volunteers aged from 40 to 60 years (mean $\pm$ SE 47 ± 5). They were essentially healthy without diabetes mellitus and hypertension, and were not taking any drugs. This study was approved by the Research Ethics Board at Sakura Hospital, Toho University. Informed consent was given and the consensus was obtained. They were administered 80 mg of metoprolol, 2 hours after breakfast. CAVI and baPWV were measured every hour for 6 hours in the supine position after a 10-minute rest each time. During the interval between measuring times, they rested in a sitting position and were prohibited to smoke and exercise. One week later, the same men were administered 4 mg doxazosin and CAVI and baPWV were measured in the same manner.

Measuring CAVI and baPWV

At measuring, a 10-minute rest was taken in the supine position. The precise methods were described in the previous report¹²⁾. Briefly, to detect brachial and ankle pulse waves using cuffs, cuff pressure was from 30 mmHg to 50 mmHg, to ensure the minimal effect of cuff pressure on hemodynamics. Blood pressure was measured after detecting the pulse.

CAVI is determined by the following equation

$$\text{CAVI} = a \{ (2\rho / \Delta P) \times \ln(P_s / P_d) \text{PWV}^2 \} + b$$

Where P_s and P_d are systolic and diastolic blood pressures, PWV is pulse wave velocity from the origin of the aorta to the junction of the tibial artery with the femoral artery, ΔP is $P_s - P_d$, ρ is blood density, and a and b are constants. CAVI is derived from β ($\beta = \ln(P_s / P_d) \cdot D / \Delta D$)^{20, 21)}, and $D / \Delta D$ is drawn from the modification of Bramwell-Hill's equation²⁾.

baPWV was calculated simultaneously⁷⁾.

These measuring tools and calculation system were equipped in VaSera (Fukuda Denshi Co. Ltd, Tokyo).

Fig. 1.

A. Effects of metoprolol on CAVI, baPWV, blood pressures and heart rate

Metoprolol (80 mg) was administered to 12 men. CAVI, baPWV, systolic blood pressure, diastolic blood pressure and heart rate were measured every hour for 6 hours.

B. Effects of doxazosin on CAVI, baPWV, blood pressure and pulse rate

Doxazosin (4 mg) was administered to 12 men. CAVI, baPWV, systolic blood pressure, diastolic blood pressure and heart rate were measured every hour for 6 hours.

Statistical analysis

The data are presented as the mean $\pm$ SE. The difference in response curves at each time point from baseline was determined by the two-tailed multiple t -test with Bonferroni correction following one-way ANOVA.

The correlations between Δ CAVI or Δ baPWV, and Δ systolic blood pressure or Δ diastolic pressure were analyzed by Spearman's correlation coefficient analysis. Significance was less than $p = 0.05$.

Results

1. Effect of metoprolol administration on blood pressure, baPWV and CAVI (Fig. 1A)

Metoprolol (80 mg) was administered to 12

men. Systolic blood pressure started to decrease at 1 hour from 131.4 ± 4.5 to 118.3 ± 4.1 mmHg (mean $\pm$ SE) ($p < 0.05$) at 3 hours and the decrease continued for 5 hours.

Diastolic blood pressure also started to decrease at 1 hour from 85.3 ± 4.0 to 75.3 ± 3.0 mmHg ($p < 0.05$) at 3 hours. The decrease continued for 6 hours.

Heart rate decreased from 70.25 ± 3.3 /min to 55.92 ± 1.8 /min at 2 hours, and returned slightly (60.4 ± 1.8 /min at 3 hours). This low heart rate continued for 6 hours.

baPWV started to decrease at 1 hour from 13.93 ± 0.46 m/sec to 12.46 ± 0.49 m/sec ($p < 0.05$) at 3 hours, significantly.

CAVI increased slightly from 8.16 ± 0.29 to 8.23 ± 0.28 at 2 hours and to 8.24 ± 0.27 at 3 hours, then

Fig. 2. Correlations between Δ CAVI and Δ baPWV, and Δ blood pressures during metoprolol administration. The differences in vascular parameters (Δ) between before and after metoprolol administration each hour were calculated and their correlation shown. A, B: Correlations between Δ CAVI, and Δ systolic pressure (A) and Δ diastolic pressure (B) during metoprolol administration. C, D: Correlations between Δ baPWV, and Δ systolic pressure (C) and Δ diastolic pressure (D) during metoprolol administration.

decreased slightly to 8.10 ± 0.27 at 5 hours ($p=0.449$), however, these changes were not statistically significant.

The differences in vascular parameters (Δ) between before and after metoprolol administration at each hour were calculated and the correlations are shown in **Fig. 2**. As shown in **Fig. 2C, D**, Δ baPWV and Δ systolic blood pressure were significantly correlated (Δ PWV = $0.856 + 0.037 \times \Delta$ sBP, $r=0.45$, $p<0.0001$), and, Δ baPWV and Δ diastolic blood pressure were also correlated significantly (Δ PWV = $0.967 + 0.025 \times \Delta$ dBp, $r=0.33$, $p=0.0046$).

The correlation between Δ CAVI and Δ systolic blood pressure and Δ diastolic blood pressure during metoprolol administration is shown in **Fig. 2A, B**. Δ CAVI and Δ systolic blood pressure were not correlated (Δ CAVI = $-0.023 + 0.002 \times \Delta$ sBP, $r=0.061$, $p=0.61$). Δ CAVI and Δ diastolic blood pressure were

also not correlated (Δ CAVI = $0.005 - 0.003 \times \Delta$ dBp, $r=-0.100$, $p=0.4044$).

Δ baPWV and Δ heart rate were correlated (Δ baPWV = $1.014 + 0.018 \times \Delta$ HR, $r=0.235$, $p=0.047$, data not shown). Δ CAVI and Δ heart rate were not correlated (Δ CAVI = $-0.012 + 0.002 \times \Delta$ HR, $r=-0.07$, $p=0.56$, data not shown).

2. Effect of doxazosin administration on blood pressure, baPWV and CAVI (Fig. 1B)

When doxazosin (4 mg) was administered to the same 12 men, one week later, mean systolic blood pressure started to decrease gradually at 1 hour from 130.2 ± 4.6 mmHg to 117.2 ± 4.8 mmHg (mean $\pm$ SE) at 3 hours ($p<0.05$), continued to decrease until 4 hours and then began to return, but was still low at 6 hours. Diastolic blood pressure started to decrease at 1 hour from 85.1 ± 4.1 mmHg to 74.2 ± 3.9 mmHg (p

Fig. 3. Correlations between Δ CAVI and Δ baPWV, and Δ blood pressures during doxazosin administration

The differences in vascular parameters (Δ) between before and after doxazosin administration each hour were calculated, and their correlation shown.

A, B: Correlations between Δ CAVI, and Δ systolic pressure (A) and Δ diastolic pressure (B) during doxazosin administration

C, D: Correlations between Δ baPWV, and Δ systolic pressure (C) and Δ diastolic pressure (D) during doxazosin administration

<0.05) at 3 hours, and continued to decrease until 5 hours, and returning slightly at 6 hours.

Heart rate started increase at 1 hour from 71.2 ± 4.4 /min to 79.3 ± 4.6 /min ($p < 0.01$) at 3 hours. The increase continued from 3 hours to 6 hours.

baPWV started to decrease at 1 hour from 13.98 ± 0.68 to 12.25 ± 0.53 m/sec at 3 hours significantly ($p < 0.05$) and returned from 5 hours.

CAVI also started to decrease at 1 hour from 8.15 ± 0.28 to 7.18 ± 0.37 ($p < 0.05$), significantly at 3 hours. This decrease continued at 4 hours and began to return from 5 hours, but was still low at 6 hours, as systolic and diastolic blood pressures decreased.

The differences in vascular parameters (Δ) between before and after doxazosin administration at each hour were calculated, and these correlations are shown in **Fig. 3**. As in **Fig. 3C, D**, Δ baPWV and Δ systolic blood pressure were significantly correlated (Δ baPWV = $0.598 + 0.029 \times \Delta$ sBP, $r = 0.281$, $p = 0.0167$).

Δ baPWV and Δ diastolic blood pressure were also significantly correlated (Δ baPWV = $0.537 + 0.035 \times \Delta$ dBp, $r = 0.337$, $p = 0.0038$).

As in **Fig. 3A, B**, Δ CAVI and Δ systolic blood pressure were significantly correlated (Δ CAVI = $0.506 + 0.023 \times \Delta$ sBP, $r = 0.31$, $p = 0.0077$), and Δ CAVI and Δ diastolic blood pressure were also significantly correlated (Δ CAVI = $0.477 + 0.026 \times \Delta$ sBP, $r = 0.351$, $p = 0.0025$).

Δ baPWV and Δ heart rate were not correlated (Δ baPWV = $0.911 + 0.001 \times \Delta$ HR, $r = 0.011$, $p = 0.927$, data not shown). Δ CAVI and Δ heart rate were negatively correlated (Δ CAVI = $0.628 - 0.024 \times \Delta$ HR, $r = 0.502$, $p < 0.0001$, data not shown).

Discussion

When metoprolol, a β -1 blocker, was administered, systolic and diastolic blood pressure decreased,

and baPWV decreased, but CAVI did not change (**Fig. 1A**). A correlation between Δ baPWV and Δ systolic and diastolic blood pressure was observed (**Fig. 2C, D**), but correlations between Δ CAVI and Δ systolic and diastolic blood pressures were not observed (**Fig. 2A, B**). These results indicate that baPWV is affected by blood pressure itself at measuring time as Nye pointed out⁵⁾, but CAVI was not affected with blood pressure changes induced by decreased heart muscle contraction. Those were confirmed by no correlations between Δ CAVI and Δ systolic and Δ diastolic blood pressures were found (**Fig. 2A, B**).

When doxazosin was administered, both baPWV and CAVI decreased as systolic and diastolic blood pressures decreased (**Fig. 1B**), and correlations between Δ CAVI and Δ systolic and Δ diastolic blood pressures were observed (**Fig. 3A, B**). CAVI appeared to be decreased by a decrease in blood pressure, but this decrease in CAVI was not directly induced by a decrease in blood pressure, because, as mentioned above, CAVI did not decrease with a decrease in blood pressure by metoprolol. The mechanism by which CAVI decreased during doxazosin administration might be due to doxazosin-induced dilatation of the arterial wall accompanying with a decrease in peripheral vascular resistance.

From these results, it was also suggested that the CAVI value itself was composed of the stiffness of matrix components such as collagen and elastin, proteoglycans^{26, 27)} and also a contraction of smooth muscle cells²⁸⁾.

The contraction of vascular smooth muscle cells is under the control of nerves and vasoconstrictive hormones, such as catecholamine²⁹⁾, angiotensin³⁰⁾, and also calcium ion³¹⁾ as vasoconstrictors, as well as nitric oxide as a vasodilator³²⁾. The precise those factors influencing CAVI should have to be studied in the future.

The dependency of CAVI on heart rate is another point of discussion. In our study, during doxazosin administration, heart rate increased, but CAVI decreased (**Fig. 1B**), and the Δ heart rate and Δ CAVI were negatively correlated; however, during metoprolol administration, the heart rate decreased for 1-2 hours, but CAVI did not change (**Fig. 1A**). It might be suggested that CAVI is independent of the heart rate in the ranges of heart rate from 55-80 beat/min.

The dependency of baPWV on heart rate (90-120 beats/min) has been reported³³⁾, and it could not be denied that baPWV was lowered partly by the decreased heart rate during metoprolol administration rather than blood pressure; however, during doxazosin administration (**Fig. 1B**), the heart rate actually in-

creased, but baPWV decreased. From our study, the relationship between baPWV and heart rate around 60-80 beats/min could not be mentioned.

In summary, our studies suggested that CAVI was independent of blood pressure at the time of measurement, and also suggested that CAVI could be affected by the changes of contractility of arterial smooth muscle cells.

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