

[ORIGINAL ARTICLE]

Endovascular Revascularization Improves the Central Hemodynamics and Augmentation Index in Patients with Peripheral Artery Disease

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Abstract:

Objective To evaluate the effect of endovascular therapy (EVT) on the central blood pressure (CBP) and augmentation index (AIx) in patients with peripheral artery disease (PAD).

Methods The CBP and AIx were assessed by radial applanation tonometry the day before and the day after EVT. We compared the differences in the therapeutic effects between the stenotic and occlusive lesions and between the iliac and superficial femoral artery (SFA) lesions.

Patients We enrolled 60 consecutive patients with PAD who underwent EVT for *de novo* lesions.

Results Both the CBP and AIx were significantly decreased after EVT (125 ± 22 mmHg to 112 ± 22 mmHg; $p=0.002$ and $84\%\pm 16\%$ to $73\%\pm 15\%$; $p<0.001$, respectively). The effects of EVT on the CBP and AIx were equivalent, regardless of whether the target lesion was the stenotic lesion or the occlusive lesion. There were no significant differences between the iliac and SFA lesions in the effects of EVT on the CBP and AIx.

Conclusion EVT improved the CBP and AIx in patients with PAD, regardless of the morphology or site of the lesions.

Key words: endovascular therapy, peripheral artery disease, central blood pressure (CBP), augmentation index (AIx)

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Introduction

Peripheral artery disease (PAD) is a global health burden with poor clinical outcomes in the aging societies (1). It is reported that patients with critical limb ischemia (CLI), which is the most advanced form of PAD, have a 20% mortality in the first year after presentation (2, 3). PAD is considered a common manifestation of atherosclerosis and is often comorbid with cerebro-cardiovascular disease, which is the major cause of its poor prognosis (4, 5).

PAD is reportedly associated with arterial stiffness, and its peripheral artery obstructions cause premature pulse wave reflections, which increase the central blood pressure (CBP)

and augmentation index (AIx) (6, 7). The CBP is the arterial pressure at the central level, such as the ascending aorta. The AIx is defined as the difference between the second and first systolic peaks, expressed as a percentage of the pulse pressure (8). The CBP is represented as the combination of the forward-traveling waves generated by left ventricular ejection and the backward-traveling reflected waves returning from the peripheral arteries, which is associated with the development of hypertensive target-organ damage (9, 10). Elevated CBP and AIx are reportedly associated with cardiovascular disease mortality (8, 11). However, the effect of endovascular revascularization on the CBP and AIx in patients with PAD remains unclear.

The aim of the present study was to assess the effect of

endovascular therapy (EVT) on the CBP and AIx in patients with PAD.

Materials and Methods

Study design and patient population

This was a cross sectional, single-center study enrolling 60 consecutive patients with PAD who underwent successful EVT for *de novo* lesions between October 2016 and June 2018. The definition of PAD was an ankle-brachial arterial pressure index (ABI) <0.9 with symptoms of lower limb ischemia. The patients who had below-the-knee lesions, cardiac arrhythmia (e.g. atrial fibrillation), and failed revascularization were excluded from this study.

EVT was performed by experienced cardiologists who followed the Trans-Atlantic Inter-Society Consensus II (TASC II) guideline recommendation (2). CBP and AIx measurements were performed the day before and the day after EVT, using an automated radial artery applanation tonometry (HEM-9000AI; Omron Healthcare, Kyoto, Japan) (12). The peripheral BP was measured at the brachial artery with Omron's inbuilt sphygmomanometer. All measurements were performed after at least 5 minutes' rest in the sitting position in a temperature-controlled room (24°C) in the morning. The major atherosclerosis risk factors, such as hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease (CKD), and smoking, were assessed. Uncontrolled hypertension is defined as a BP that remains above 140/90 mmHg despite the use of 3 antihypertensive agents of different classes (13). Smoking included both current and past smokers. The clinical data were obtained based on the medical records or a history of medical therapy, and medications were assessed at admission.

The timing of the backward-reflected waves is affected by the distance between the heart and the reflection site (14). Therefore, we compared the difference in the therapeutic impact of revascularization on the CBP and AIx between iliac and superficial femoral artery (SFA) lesions.

The study protocol was approved by institutional ethics committee and all patients provided their written informed consent.

Statistical analyses

The results are expressed as the mean \pm standard deviation for continuous variables and as percentages for categorical variables. Skewed values are presented as the median and interquartile range (IQR). The predictors of improvement in the CBP and AIx were analyzed by a linear regression analysis. Correlations among the Δ CBP, Δ AIx, and Δ ABI were analyzed by using Pearson's correlation coefficient. We used *t*-tests and chi-square tests to compare continuous and categorical variables, respectively. If the data were not normally distributed, the Mann-Whitney U-test was employed. A *p* value of <0.05 was considered statistically significant. All statistical analyses were performed with a

standard software package (JMP version 12; SAS institute, Cary, USA).

Results

Baseline characteristics and the comparison of clinical characteristics between iliac and SFA lesions

Table 1 shows the baseline characteristics of the study population. There were 52 men and 8 women, and the mean age was 73 \pm 8 years old. There were 11 (18%) patients with CLI. Hypertension, diabetes mellitus, dyslipidemia, and CKD were identified in 49 (82%), 20 (33%), 37 (62%), and 26 (43%) patients, respectively. The SFA lesion group had significantly higher prevalence rates of CKD and hemodialysis than the iliac lesion group. There were no significant differences in the prevalence rates of hypertension, diabetes mellitus, dyslipidemia, previous ischemic heart disease, previous stroke, or medications, excluding aldosterone blockers, between the iliac and SFA lesions.

The impact of EVT on the CBP and AIx in patients with PAD

As shown in Fig. 1A, B, both the CBP and AIx were significantly improved after EVT (125 \pm 22 mmHg to 112 \pm 22 mmHg; *p*=0.002 and 84% \pm 16% to 73% \pm 15%; *p*<0.001, respectively). The effects of EVT on the CBP and AIx were equivalent, regardless of whether the target lesion was the stenotic lesion (Fig. 2A, B) or the occlusive lesion (Fig. 2C, D). In addition, the peripheral BP measured in the upper arm was also significantly reduced after EVT (Table 2).

The comparison of the effects of EVT between iliac and SFA lesions

The comparison of the lesion characteristics between the iliac and SFA lesions is shown in Table 3. Chronic total occlusion was noted in 11 (37%) iliac lesions and 20 (67%) SFA lesions. There were no significant differences in TASC II category C or D, the proportion of stent use, or number of stents between the groups. The SFA lesion group had a significantly longer lesion length, whereas the iliac lesion group had a significantly larger stent size. As Fig. 3 show, the effects of the EVT on CBP and AIx were not significantly different between the iliac and SFA lesions (-12 mmHg vs. -15 mmHg; *p*=0.537, and -11% vs. -10%; *p*=0.745, respectively).

The factors associated with improvement in the CBP and AIx by EVT

The factors associated with improvement of the CBP and AIx are detailed in Table 4. A higher pre-EVT CBP was associated with a greater decrease in the CBP after EVT (β =-0.454; *p*<0.001). Similarly, a higher pre-EVT AIx was associated with a greater decrease in AIx after EVT (β =-0.462; *p*<0.001). TASC II category C or D was associated

Table 1. Baseline Characteristics and the Comparison of Clinical Characteristics between the Iliac and SFA Lesions.

Variables	All patients n=60	Iliac lesions n=30	SFA lesions n=30	p value
Age (years old)	73±8	72±7	74±8	0.315
Men / Women	52 / 8	24 / 6	28 / 2	0.121
BMI (kg/m ²)	23.1±3.6	23.6±4.0	22.7±3.2	0.390
Claudication (Rutherford 2 or 3), n (%)	49 (82)	25 (83)	24 (80)	0.739
Critical limb ischemia (Rutherford 4-6), n (%)	11 (18)	5 (17)	6 (20)	0.739
pre-ABI	0.57±0.22	0.57±0.24	0.57±0.21	0.991
post-ABI	0.90±0.15	0.90±0.16	0.90±0.14	0.852
Hypertension, n (%)	49 (82)	24 (80)	25 (83)	0.739
Diabetes mellitus, n (%)	20 (33)	10 (33)	10 (33)	1.000
Dyslipidemia, n (%)	37 (62)	19 (63)	18 (60)	0.791
CKD, n (%)	26 (43)	9 (30)	17 (57)	0.036
Hemodialysis, n (%)	12 (20)	3 (10)	9 (30)	0.049
Previous IHD, n (%)	23 (38)	11 (37)	12 (40)	0.791
Previous stroke, n (%)	15 (25)	7 (23)	8 (27)	0.766
Uncontrolled hypertension, n (%)	6 (10)	3 (10)	3 (10)	1.000
Smoking, n (%)	55 (92)	27 (90)	28 (93)	0.639
Number of antiplatelet agents	1.9±0.3	1.9±0.4	1.9±0.3	0.703
Number of antihypertensive agents	1.8±1.0	1.7±1.0	1.8±0.9	0.502
Blood examination				
eGFR (mL/min/1.73 m ²)	56.7±33.0	63.9±29.2	49.5±35.5	0.098
Triglycerides (mg/dL)	132.9±79.8	143.2±88.1	122.5±70.5	0.327
LDL-C (mg/dL)	93.7±30.0	97.2±25.2	90.1±34.1	0.369
HDL-C (mg/dL)	51.4±16.9	49.2±17.4	53.5±16.4	0.339
HbA1c (%)	6.3±0.8	6.3±0.7	6.3±1.0	0.913
BNP (pg/mL)	44.4 (11.6 - 129.9)	42.0 (9.9 - 74.2)	53.5 (13.7 - 176.5)	0.390
hs-CRP (mg/dL)	0.11 (0.05 - 0.21)	0.11 (0.03 - 0.20)	0.11 (0.06 - 0.30)	0.102
Medications				
ACEIs and/or ARBs, n (%)	47 (78)	23 (77)	24 (80)	0.754
CCBs, n (%)	40 (67)	18 (60)	22 (73)	0.272
β-blockers, n (%)	18 (30)	9 (30)	9 (30)	1.000
Statins, n (%)	40 (67)	18 (60)	22 (73)	0.272
Nitrates, n (%)	9 (15)	3 (10)	6 (20)	0.274
Aldosterone blockers, n (%)	7 (12)	1 (3)	6 (20)	0.035
Aspirin, n (%)	41 (68)	21 (70)	20 (67)	0.781
Clopidogrel, n (%)	55 (92)	27 (90)	28 (93)	0.639
Cilostazol, n (%)	15 (25)	5 (17)	10 (33)	0.133

Data are expressed as mean±SD, number (percentage), or median (interquartile range).

ABI: ankle-brachial arterial pressure index, ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, BMI: body mass index, BNP: B-type natriuretic peptide, CCBs: calcium-channel blockers, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, HbA1c: hemoglobin A1c, HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, IHD: ischemic heart disease, LDL-C: low-density lipoprotein cholesterol, SFA: superficial femoral artery

with a greater decrease in AIx after EVT ($\beta=-0.279$; $p=0.031$). As shown in Fig. 4, the patients with TASC II category C or D had significantly greater decrease in AIx after EVT than those with TASC II category A or B (-7 mmHg vs. -14 mmHg; $p=0.031$). Fig. 5A and B show the correlations among Δ CBP, Δ AIx, and Δ ABI. Intriguingly, there was no significant correlation between Δ CBP and Δ ABI, while Δ AIx tended to be correlated with Δ ABI, although the correlation did not reach statistical significance. As expected, there was a significant positive correlation between Δ CBP and Δ AIx (Fig. 5C).

Discussion

Main findings

The main findings of this study were as follows: 1) Both the CBP and AIx were significantly improved after EVT, regardless of whether the target lesion was the stenotic lesion or the occlusive lesion; 2) There were no significant differences in the effects of EVT on the CBP or AIx between the iliac and SFA lesions; 3) Patients with a higher CBP were more likely to enjoy an improvement in their CBP, and patients with a higher AIx were similarly more likely to enjoy

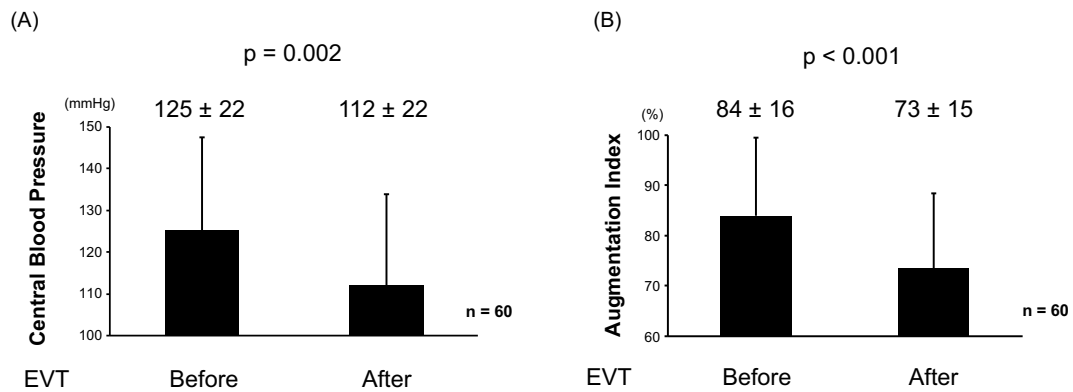


Figure 1. (A) The impact of EVT on the CBP. (B) The impact of EVT on the AIx. AIx: augmentation index, CBP: central blood pressure, EVT: endovascular therapy

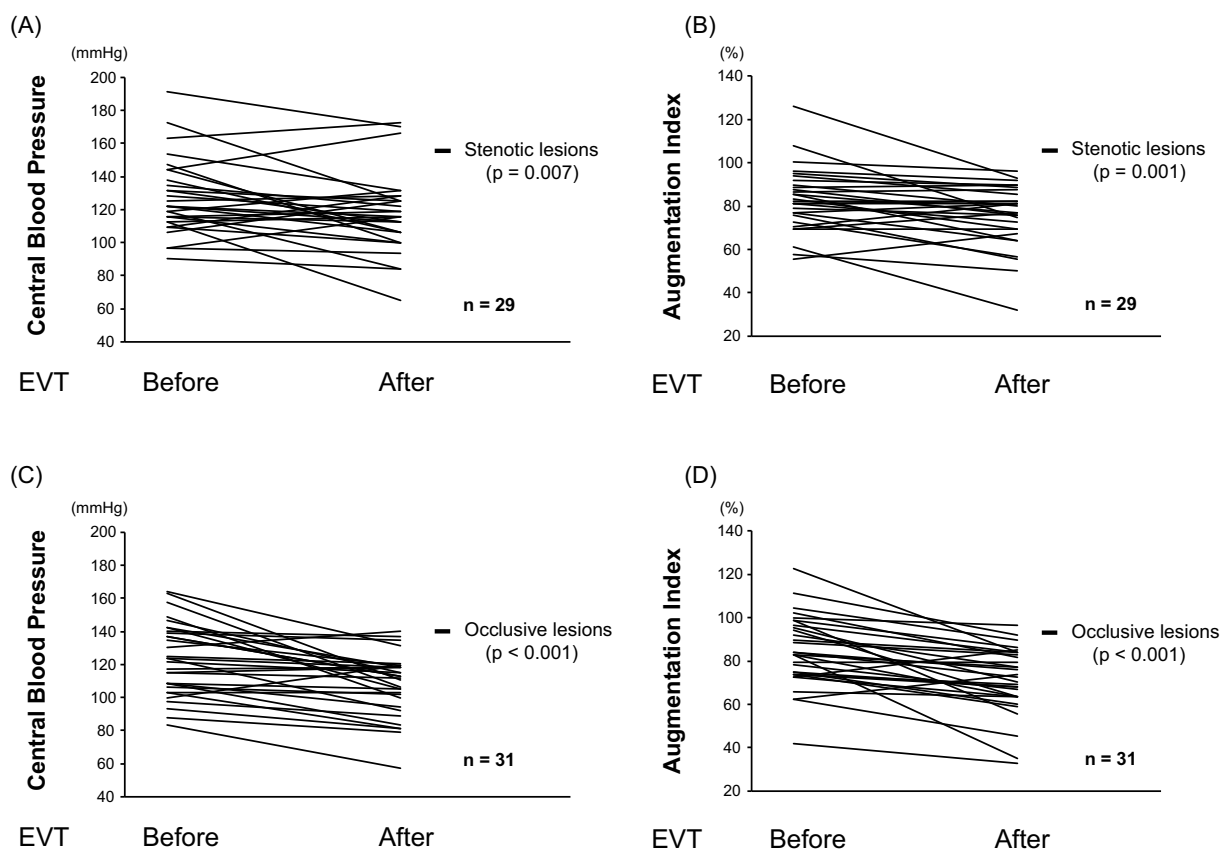


Figure 2. (A) The impact of EVT on the CBP in stenotic lesions. (B) The impact of EVT on the AIx in stenotic lesions. (C) The impact of EVT on the CBP in occlusive lesions. (D) The impact of EVT on the AIx in occlusive lesions. AIx: augmentation index, CBP: central blood pressure, EVT: endovascular therapy

an improvement in their AIx after EVT. Furthermore, patients with TASC II category C or D were more likely to enjoy an improvement in their AIx than those with TASC II category A or B after EVT.

The effect of EVT on the CBP and AIx

It was previously reported that EVT was associated with a reduction in the AIx at three months after revascularization, which was caused by an increase in the physical activity due

to reducing claudication symptoms (15, 16). However, our results showed that EVT induced an immediate reduction in both the CBP and AIx, surprisingly on the day after EVT.

Several potential mechanisms whereby endovascular reperfusion was associated with the improvement in both the CBP and AIx may be speculated. The presence of lower limb arterial stenoses and obstructions can alter the timing and amplitude of the backward-reflected waves (10). Consequently, the premature reflection pulse waves during late

systole can increase the central pressure augmentation. Although we cannot measure the precise timing of backward-reflected waves directly, the AIX decreased immediately after EVT. Therefore, it is reasonable to conclude that EVT ameliorated the premature pulse wave reflections by improving the impairment of lower limb perfusion. In addition, EVT can increase the vascular bed capacity, which is decreased by peripheral artery obstructions in patients with PAD. The increase in the vascular capacity due to EVT can contribute

to a decrease in the total systemic resistance and a subsequent decrease in the CBP.

Furthermore, it has been reported that recanalization of an occluded infarct artery triggered inflammatory responses by releasing cytokines, such as tumor necrosis factor (TNF)- α and interleukin (IL)-1, which caused reperfusion injury (17). Inflammatory cytokines can produce inducible nitric oxide synthase (iNOS), generating large amounts of nitric oxide (NO) (18). In addition to this, inflammatory mediators, such as prostaglandins and bradykinins, are associated with vascular permeability and vasodilation (19). We can therefore assume that these vasodilator substances reduce arterial stiffness and subsequently the AIX, which might lead to the reduction in the CBP.

Although the distance between the heart and the reflection site was longer in the iliac lesion group than in the SFA lesion group, our results showed that the reductions in the CBP and AIX were not significantly different between the iliac and SFA lesions. It has been shown that the backward-reflected waves are generated by not only the bifurcation of the large artery but also the myriad terminations of low-resistance arteries into high-resistance arterioles (20). This arterial conducting mechanism may thus explain how EVT

Table 2. The Impact of EVT on Peripheral Blood Pressure in Patients with PAD.

Variables	Pre-EVT n=60	Post-EVT n=60	p value
Peripheral SBP (mmHg)	138 \pm 20	130 \pm 20	0.024
Peripheral DBP (mmHg)	67 \pm 13	62 \pm 12	0.055
Peripheral MBP (mmHg)	91 \pm 12	84 \pm 13	0.015
Pulse pressure (mmHg)	72 \pm 18	68 \pm 18	0.238
Heart rate (bpm)	71 \pm 18	72 \pm 13	0.818

Data are expressed as mean \pm SD.

DBP: diastolic blood pressure, EVT: endovascular therapy, MBP: mean blood pressure, PAD: peripheral artery disease, SBP: systolic blood pressure

Table 3. The Comparison of Lesion Characteristics between the Iliac and SFA Lesions.

Variables	All patients n=60	Iliac lesions n=30	SFA lesions n=30	p value
Chronic total occlusion, n (%)	31 (52)	11 (37)	20 (67)	0.019
Lesion length (mm)	121 \pm 88	90 \pm 83	151 \pm 85	0.007
TASC II category C/D, n (%)	27 (45)	12 (40)	15 (50)	0.436
Stent use, n (%)	58 (97)	30 (100)	28 (93)	0.092
Mean stent diameter (mm)	7.4 \pm 1.3	8.3 \pm 1.2	6.5 \pm 0.6	<0.001
Number of stents	1.7 \pm 0.8	1.7 \pm 0.7	1.7 \pm 0.9	1.000

Data are expressed as mean \pm SD, number (percentage).

SFA: superficial femoral artery

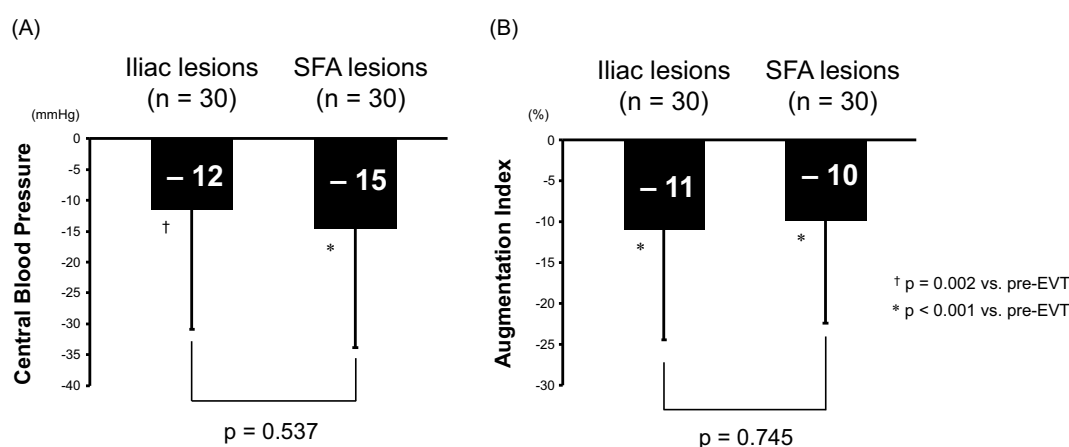


Figure 3. (A) The comparison of the effects of EVT on the CBP between the iliac and SFA lesions. (B) The comparison of the effects of EVT on the AIX between the iliac and SFA lesions. AIX: augmentation index, CBP: central blood pressure, EVT: endovascular therapy, SFA: superficial femoral artery

Table 4. The Factors Associated with Improvement in the CBP and AIx.

	CBP			AIx		
	Standardized Coefficient (beta)	R ²	p value	Standardized Coefficient (beta)	R ²	p value
Age	0.072	0.005	0.586	-0.010	<0.001	0.942
Male gender	-0.132	0.017	0.315	-0.048	0.002	0.715
BMI	-0.214	0.046	0.104	-0.212	0.045	0.106
CLI	-0.231	0.053	0.076	-0.229	0.052	0.079
Pre-EVT ABI	-0.058	0.003	0.660	0.102	0.010	0.438
Iliac lesion	0.081	0.007	0.537	-0.043	0.002	0.745
Chronic total occlusion	-0.151	0.023	0.249	-0.224	0.050	0.086
Lesion length	-0.069	0.005	0.599	-0.124	0.015	0.345
TASC II category C/D	-0.128	0.016	0.332	-0.279	0.078	0.031
Stent use	0.082	0.007	0.532	-0.188	0.035	0.151
Mean stent diameter	0.109	0.012	0.417	0.049	0.002	0.714
Number of stents	-0.062	0.004	0.639	0.158	0.025	0.229
Pre-EVT CBP	-0.454	0.206	<0.001	-0.202	0.041	0.122
Pre-EVT AIx	-0.218	0.047	0.095	-0.462	0.214	<0.001

ABI: ankle-brachial arterial pressure index, AIx: augmentation index, BMI: body mass index, CBP: central blood pressure, CLI: critical limb ischemia, EVT: endovascular therapy

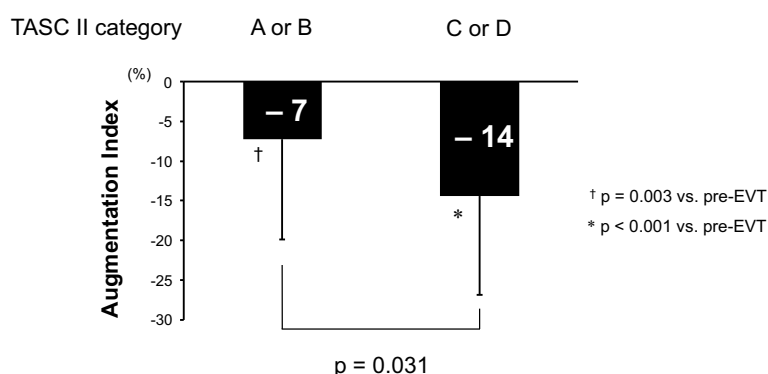


Figure 4. The comparison of the effects of EVT on the AIx between TASC II category A/B and C/D. AIx: augmentation index, EVT: endovascular therapy

improved both the CBP and AIx, regardless of whether the target lesion was an iliac lesion or SFA lesion, in the present study.

The predictors of the effects of EVT on CBP and AIx

The patients who showed an improvement in the CBP after EVT had a significantly higher pre-EVT CBP than those who had a lower pre-EVT CBP, and similarly, the patients who showed an improvement in the AIx after EVT had a significantly higher pre-EVT AIx than those who had a lower pre-EVT AIx, suggesting that the patients with higher CBP or AIx values may benefit more from EVT than those with lower values. In addition, the patients with TASC II category C or D showed a greater improvement in the AIx than those with TASC II category A or B. Since TASC II category C or D lesions were longer than those in TASC II category A or B, the timing of the backward-reflected waves may have been more delayed after EVT. In the present study population, the patients with TASC II category C or D

had a significantly higher prevalence of CLI than those with TASC II category A or B (33% vs. 9%; p=0.006). Previous studies have shown that CLI is associated with microvascular dysfunction as well as macrovascular dysfunction (21), which can lead to an increase in the AIx and subsequent greater efficacy of EVT.

Clinical implications

There is no certain evidence proving the prognostic value of EVT, even in the patients with CLI (22). However, it has been reported that PAD is associated with an increase in the CBP and AIx and an increased risk of cardiovascular events (7, 23). Furthermore, previous studies showed that the CBP was more strongly associated with cardiovascular events than the brachial BP (24, 25). Given these findings, EVT may help improve cardiovascular disease mortality and the prognosis of patients with PAD by reducing the CBP and AIx.

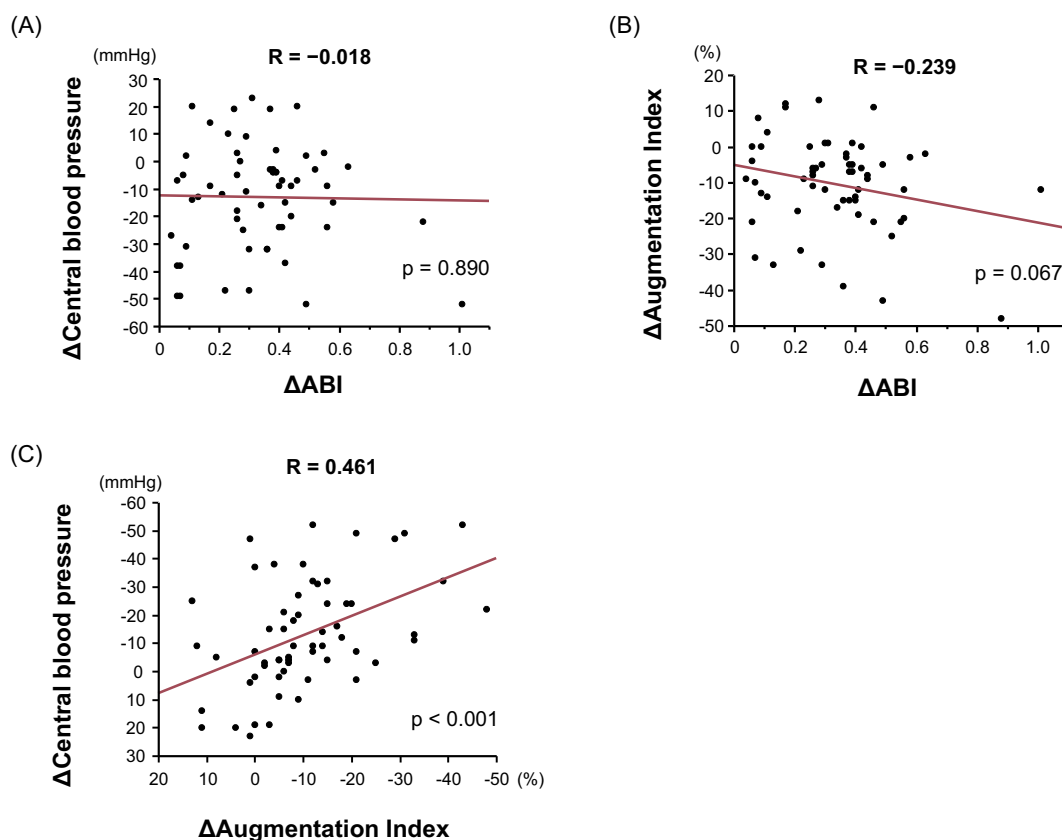


Figure 5. (A) The correlation between the Δ CBP and Δ ABI. (B) The correlation between Δ AIx and Δ ABI. (C) The correlation between Δ CBP and Δ AIx. ABI: ankle-brachial pressure index, AIx: augmentation index, CBP: central blood pressure

Limitations

Several limitations associated with the present study warrant mention. First, this study was a single-center observational study. Second, the study population was relatively small in the present investigation. Third, since most of this study subjects were men, we could not evaluate the gender differences in the AIx. Finally, the CBP and AIx values after EVT were only measured on the day after EVT.

Conclusion

EVT improved the CBP and AIx in patients with PAD, regardless of the morphology or site of the lesions.

The authors state that they have no Conflict of Interest (COI).

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