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ORIGINAL ARTICLE
Peripheral Vascular Disease

Impact of Endovascular Therapy on Oxidative Stress in Patients With Peripheral Artery Disease

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Background: Atherosclerosis is believed to be caused by oxidative stress. Endovascular therapy (EVT) is effective for claudication of patients with peripheral artery disease (PAD). However, its effect on oxidative stress in PAD patients is unknown. Here, the impact of EVT on oxidative stress in PAD patients is investigated.

Methods and Results: Twenty-five PAD patients (Rutherford stage II or III) who underwent EVT were enrolled. The levels of diacron-reactive oxygen metabolite (d-ROM; an oxidative stress marker), ankle-brachial index (ABI), and maximum walking distance at baseline and at 3 months after EVT were measured. As compared with baseline values, the maximum walking distance and ABI improved significantly after EVT (109.9±104.2 vs. 313.7±271.8 m, P<0.0001; 0.61±0.15 vs. 0.91±0.13 m, P<0.0001, respectively). The improved exercise capacity and arterial flow induced a significant decrease in d-ROM levels (from 472.8±64.8 to 390.2±46.7 U.CARR; P<0.0001). The decrease in d-ROM levels after EVT was more prominent in PAD patients with a high baseline d-ROM level. The increased ABI (r=0.524, P=0.0007) and maximum walking distance (r=–0.416, P=0.039) after EVT were significantly correlated with the decreased d-ROM levels.

Conclusions: The improved exercise capacity and peripheral blood flow induced by EVT decreases oxidative stress in PAD patients. (*Circ J* 2014; **78:** 1445–1450)

Key Words: Exercise; Oxidative stress; Peripheral artery disease; Revascularization

Atherosclerosis is a systemic disease that affects all major vascular territories. Peripheral artery disease (PAD) is an atherosclerotic disease affecting mainly the lower extremities that causes atherosclerosis, and its incidence continues to increase worldwide.[1,2] This disorder affects 8–12 million individuals in the U.S. and is increasingly prevalent in Europe and Asia.[3] Endovascular therapy (EVT) has been established as a primary therapy for patients with PAD.[4–8] The purpose of EVT is to improve walking distance and leg symptoms, including intermittent claudication and resting leg pain.[9] EVT and optimal medical treatment can result in the improvement of leg symptoms in most patients. However, PAD patients often have atherosclerosis-related complications, such as coronary artery disease and cerebrovascular disease, which affect the overall mortality.[10] In the REACH registry, the rate of complications for patients with coronary artery disease and cerebrovascular disease was 38.5% and 9.8%, respectively, with a combined complication rate of 13.1%.[11] Revascularization therapy, including EVT, is considered to be limited to the vascular bed; therefore, it is thought that EVT cannot prevent the development of other systemic vascular bed diseases.

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The association between oxidative stress and the development of atherosclerosis has been investigated in several recent reports.[12] Oxidative stress plays many roles in the pathophysiology of atherosclerosis, including dyslipidemia, which leads to atheroma formation, diabetes mellitus, endothelial dysfunction, plaque rupture, and myocardial ischemic injury.[13] Furthermore, it is correlated with metabolic syndrome, which is a known risk factor for atherosclerosis.[14,15] Moreover, metabolic syndrome is correlated with symptomatic and functional outcomes in PAD patients.[16] Oxidative stress could serve as both an etiological factor as well as a predictor for atherosclerosis.[17,18] However, the strategies for improving oxidative stress using antioxidant agents remain unclear. Performing appropriate exercise has been reported to be effective in improving oxidative stress.[19] Semba et al described a correlation between oxidative stress and walking disability among older women.[20]

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$$R\text{-}OOH + Fe^{2+} \rightarrow R\text{-}O + Fe^{3+} + OH^-$$
$$R\text{-}O^- + A\text{-}NH_2 \rightarrow R\text{-}O^- + [A\text{-}NH2^-]^+$$
$$R\text{-}OOH + Fe^{3+} \rightarrow R\text{-}OO^- + Fe^{2+} + H^+$$
$$R\text{-}OO^- + A\text{-}NH2 \rightarrow R\text{-}OO^- + [A\text{-}NH2^*]^+$$

Figure 1. Chemical reactions involved in the d-ROM test. d-ROM, diacron-reactive oxygen metabolite.

However, PAD patients show a decreased walking capacity due to the presence of leg pain.[21,22] Thus, impaired walking capacity in PAD patients might increase their oxidative stress levels.

With regard to patients with PAD who exhibit intermittent claudication, EVT has been shown to effectively increase walking capacity. Impaired walking ability has several important clinical implications. Diminished physical activity in daily life predicts higher overall mortality in patients with PAD.[23–25] Functional measures including the 6-min walk test and treadmill walking time have been associated with increased mortality and risk of cardiovascular events in patients with PAD.[26–29] Together, these findings suggest that EVT and augment exercise performance in patients with PAD might have a wide-range of healthy benefits. However, it is not clear whether EVT additionally contributes to a reduction in the cardiovascular risk, which is a major therapeutic goal in PAD patients.

We hypothesize that improved exercise capacity, induced by EVT, decreases the oxidative stress level in PAD patients. Therefore, in the present study, we investigated the effects of EVT on oxidative stress and the relationship between the changes in oxidative stress levels and the maximum walking distance in PAD patients.

Methods

Patient Population

A total of 25 patients with PAD who underwent EVT in our institution were enrolled in this retrospective study. All the patients experienced intermittent claudication (Rutherford stage II and III). Patients were excluded if they had untreated coronary artery disease, symptomatic heart failure, or cancer. Patients who required hemodialysis were also excluded, because hemodialysis has been reported to affect oxidative stress levels.[30] We evaluated the medication history before and after EVT; these were observed to be unchanged. The medication history was evaluated because certain medical agents can influence oxidative stress.[31]

Sampling and Measurement

We determined the levels of diacron-reactive oxygen metabolite (d-ROM), a marker of oxidative stress, from the venous serum samples collected just before and at 3 months after EVT. The d-ROM level is known to be proportional to the serum hydroperoxide concentration (Figure 1).[32] Hydroperoxides are the peroxidation products of proteins, peptides, amino acids, lipids, and fatty acids. In the presence of peroxides, the measurement of the d-ROM level is based on the ability of transition metals to catalyze the formation of free radicals, which are trapped by an alkylamine. The alkylamine reacts to form a colored radical that can be detected at 505 nm. The d-ROM levels were determined by the Free Radical Elective Evaluator (Diacron International, Grosseto, Italy) using commercial assay kits (Diacron Intermnational srl, Grosseto, Italy). The results are expressed in conventional units called U.CARR (Carratelli units; 1 U.CARR corresponds to 0.8 mg/L H_2O_2). The d-ROM level in 25 healthy male control subjects (age 65.5±5.6 years) from our institution is 367.7±56.2 U.CARR.

We also measured the ankle-brachial index (ABI) using the FORM ABI/PWV (Omron Colin Co, Japan). The FORM ABI/PWV is a device with 4 cuffs that can measure blood pressure levels simultaneously in both arms and both legs, and automatically calculates the ABI. Maximum walking distance was measured by using the treadmill test (12% incline at 2.4 km/h) before and at 3 months after EVT.

Statistical Analysis

Continuous variables are presented as mean±standard deviation, and categorical variables are expressed as a number and

Table 1. Baseline Characteristics of All Patients

	Value
Number of patients	25
Age (years)	73.6±7.14
Male	23 (92.0)
Hypertension	20 (80.0)
Dyslipidemia	17 (68.0)
Diabetes mellitus	10 (40.0)
Smoking	21 (84.0)
CKD	4 (16.0)
CAD	13 (52.0)
CVD	3 (12.0)
Rutherford classification	
II	4 (16.0)
III	21 (84.0)
Hemoglobin (g/dl)	14.07±1.86
Serum creatinine (mg/dl)	0.93±0.40
eGFR ($mL \cdot min^{-1} \cdot 1.73\,cm^{-2}$)	63.16±20.58
Serum LDL-C (mg/dl)	98.80±34.06
Serum HDL-C(mg/dl)	52.88±11.81
HbA1c (%)	6.06±1.04
C-reactive protein (mg/dl)	0.28±0.37
Maximum walking distance (m)	109.9±104.2
ABI	0.61±0.15
d-ROM (U.CARR)	472.8±64.8
Medical therapies	
Aspirin	20 (80)
Clopidogrel	9 (36)
Cilostazol	16 (64)
Statins	17 (68)
Calcium channel blocker	13 (52)
ACEI/ARB	12 (48)
β-receptor blockers	5 (20)

Values are presented as number (percentage) or mean±standard deviation.
ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; d-ROM, diacron-reactive oxygen metabolite; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

percentage. Continuous variables were compared using the 2-sided paired *t*-test, and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The relationship between the continuous variables was investigated using Pearson's correlation coefficient test. Results with a $P<0.05$ and a $r>0.4$ were considered to be statistically significant. All analyses were performed using SPSS statistical software, version 13.0 (SPSS Inc, Chicago, Illinois, USA).

Results

The baseline characteristics of the patients are described in Table 1. The average age of the 25 patients was 73.6±7.1 years, and 23 patients (92%) were male. Hypertension was observed in 20 patients (80%), dyslipidemia was observed in 17 patients (68%), and diabetes mellitus (DM) was observed in 10 patients (40%). A history of smoking was recorded in 21 patients (84%). Moreover, chronic kidney disease was observed in 4 patients (16%); for all the patients, the average serum creatinine level was 0.93±0.40 mg/dl and the estimated glomerular filtrated rate was 63.16±20.58 $ml \cdot min^{-1} \cdot 1.73\,cm^{-2}$. With regard to intermittent claudication, 4 (16%) and 21 (86%) out of 25 patients were classified as Rutherford stage II and III, respectively. The average ABI and maximum walking distance values were 0.61±0.15 and 109.9±104.2 m, respectively.

Table 2 describes the characteristics of the target lesions. Of all the target lesions, 14 (56%) were present in the iliac artery (56%) and 11 (44%) were present in the superficial femoral artery. Moreover, based on the classification of the TransAtlantic Inter-Society Consensus II (TASC II), 7 lesions (28%) were Type A, 2 lesions (8%) were Type B, 5 lesions (20%) were Type C, and 11 lesions (44%) were Type D. The average lesion length and lesion width were 97.2±61.4 mm and 6.04±1.17 mm, respectively. All of the patients underwent stenting.

Table 3 shows a comparison of clinical parameters before

Table 2. Baseline Target Lesion Characteristics of All Patients

Number of patients	25
Target lesion location	
Iliac artery	14 (56%)
Superficial femoral artery	11 (44%)
TASC II (IA, SFA)/(%)	
Type A	7 (5,2)/28%
Type B	2 (0,2)/8%
Type C	5 (3,2)/20%
Type D	11 (6,5)/44%
Lesion length (mm)	97.2±61.4
Lesion width (mm)	6.04±1.17
Stenting	25 (100%)
Stent width (mm)	8.3±1.3
Stent length (mm)	101.3±66.1

Values are presented as number (percentage) or mean±standard deviation.
IA, Iliac artery; SFA, superficial femoral artery; TASC II, TransAtlantic Inter-Society Consensus II.

Table 3. Comparison of the Clinical Characteristics Before and 3 Months After EVT

	Before EVT	Post EVT	P value
C-reactive protein (mg/dl)	0.28±0.37	0.26±0.50	0.616
Serum creatinine (mg/dl)	0.93±0.40	0.98±0.49	0.071
Hemoglobin (g/dl)	14.07±1.86	13.49±1.83	0.167
Maximum walking distance (m)	109.9±104.2	313.7±271.8	<0.0001
ABI	0.61±0.15	0.91±0.13	<0.0001
d-ROM (U.CARR)	472.8±64.8	390.2±46.7	<0.0001

Values are presented as mean±standard deviation.
EVT, endovascular therapy. Other abbreviations as in Table 1.

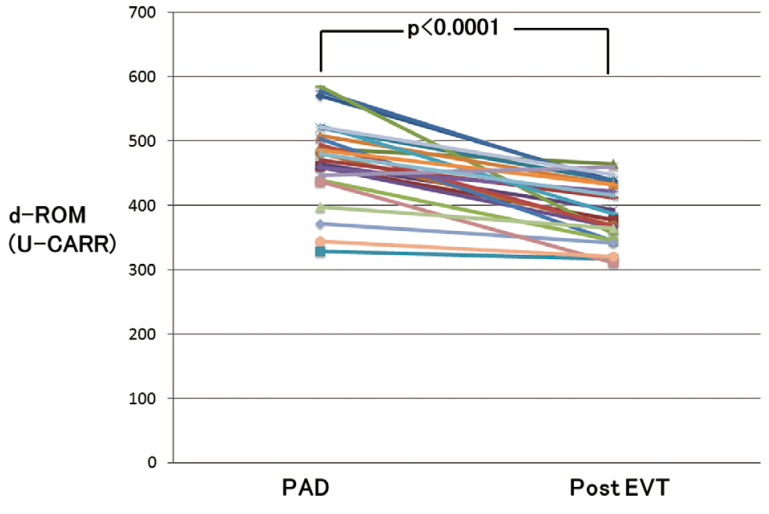

Figure 2. Comparison of d-ROM levels before and at 3 months after EVT. The d-ROM levels decreased significantly at 3 months after EVT as compared with the baseline levels (390.2±46.7 U.CARR vs. 472.8±64.8 U.CARR, $P<0.0001$, respectively). d-ROM, diacron-reactive oxygen metabolite; EVT, endovascular therapy.

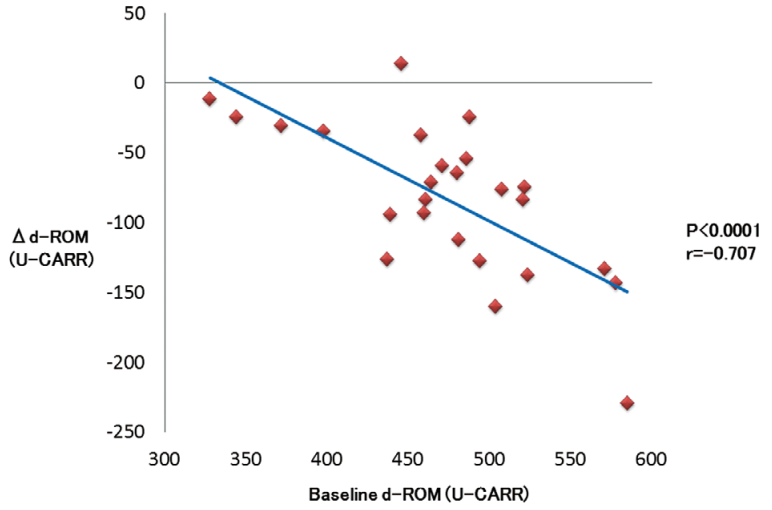

Figure 3. Correlation between delta d-ROM and baseline d-ROM. The differences in the d-ROM levels before (at baseline) and at 3 months after EVT were correlated with the baseline d-ROM levels (P<0.0001, r=0.707). d-ROM, diacron-reactive oxygen metabolite; EVT, endovascular therapy.

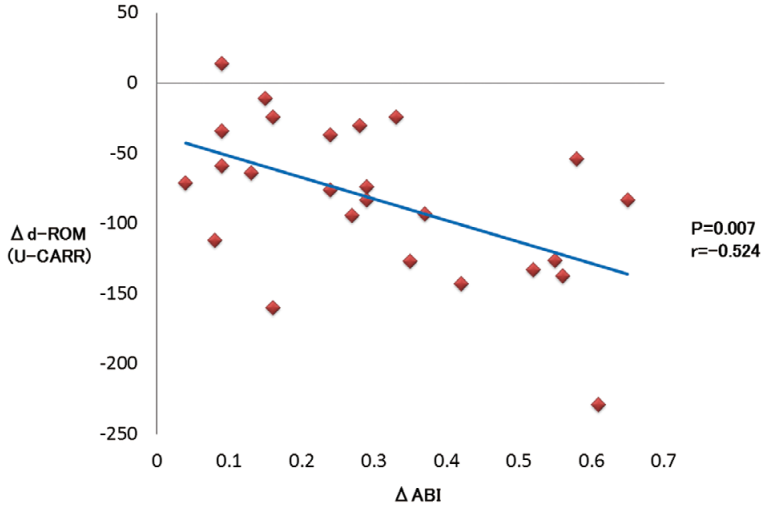

Figure 4. Correlation between delta d-ROM and delta ABI. The differences in the d-ROM levels before (at baseline) and at 3 months after EVT were significantly correlated with the differences in ABI before (at baseline) and at 3 months after EVT (P=0.007, r=0.524). d-ROM, diacron-reactive oxygen metabolite; ABI, ankle-brachial index; EVT, endovascular therapy.

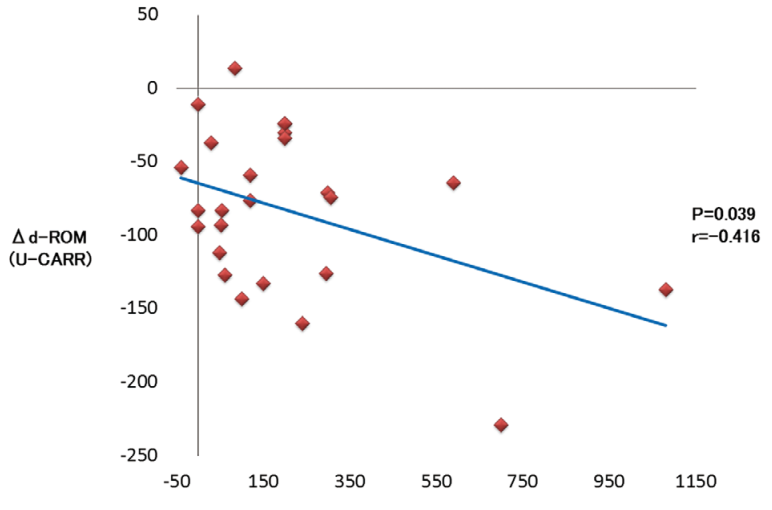

Figure 5. Correlation between delta d-ROM and delta walking distance. The differences in the d-ROM levels before (at baseline) and at 3 months after EVT were correlated with the differences in walking distance before (at baseline) and at 3 months after EVT (P=0.039, r=0.416). d-ROM, diacron-reactive oxygen metabolite; EVT, endovascular therapy.

and at 3 months after EVT. The serum C reactive protein (CRP), serum creatinine, and hemoglobin levels before EVT did not significantly differ from those at 3 months after EVT. However, the maximum walking distance and ABI values increased significantly at 3 months after EVT as compared to the values before EVT. At baseline, the d-ROM level in PAD patients (472.8±64.8 U.CARR) were higher than the d-ROM levels in healthy control subjects (367.7±56.2 U.CARR); however, the d-ROM levels decreased significantly at 3 months after EVT (472.8±64.8 vs. 390.2±46.7 U.CARR, P<0.0001; **Figure 2**).

A delta value was defined as the difference in the value before (at baseline) and after EVT. As shown in **Figure 3**, we observed a significant negative correlation between delta d-ROM levels and baseline d-ROM levels (P<0.0001, r=0.707). The decrease in d-ROM levels was more prominent in patients with a higher baseline d-ROM level.

The correlation between delta d-ROM and delta ABI is shown in **Figure 4**. The increased ABI level at 3 months after EVT was significantly correlated with the decreased d-ROM level at 3 months after EVT (P=0.007, r=0.524). **Figure 5** shows the correlation between delta d-ROM and the delta maximum walking distance. The improvement in the maximum walking distance at 3 months after EVT was significantly correlated with the decreased d-ROM levels (P=0.039, r=–0.416).

Discussion

In the present study, we showed that EVT successfully improved maximum walking distance and ABI in PAD patients. We also demonstrated that their oxidative status – as indicated by the d-ROM levels – was significantly improved after EVT and that the changes in oxidative stress levels were significantly associated with the improvement in the maximum walking distance and ABI.

With the evolution of the EVT technique, the number of patients undergoing EVT has increased, making it a commonly performed procedure in recent times. Increasing evidence suggests that the primary and long-term patency rate achieved with nitinol stents for iliac and superficial femoral arterial lesions is superior to that achieved by conventional balloon angioplasty alone.[33–35] EVT is known to improve the symptoms of PAD patients, including intermittent claudication and resting leg pain. After undergoing EVT, the patients can reportedly walk longer distances, mainly due to improvement in intermittent claudication. In the present study, we were able to describe an additional beneficial effect of EVT on the oxidative status of these patients. To the best of our knowledge, this is the first study to show that EVT improves oxidative status in PAD patients.

Oxidative stress is caused by an imbalance between the generation of reactive oxygen species (ROS) and the capacity of the antioxidant defense system.[36] Although there is a lack of appropriate epidemiological markers to measure oxidative stress, a few markers have been examined specifically with respect to PAD. In the present study, we used the d-ROM test, which facilitates the measurement of hydroperoxides, to detect the level of oxidative stress. The usefulness of the d-ROM test for evaluating the correlation between increased levels of systemic inflammation and oxidative stress has been reported in previous clinical studies.[37,38] As compared to other conceptually similar tests for assessing oxidative status in plasma samples, d-ROM test values correlate directly and significantly with plasma 8-isoprostane levels in healthy subjects.[39] A highly significant positive correlation has also been found between the d-ROM test and the FOX assay, a well-established test for plasma lipid hydroperoxides, in controls and hemodialysed patients.[40] Therefore, in this study, we used the d-ROM test to investigate the effect of EVT on oxidative status in PAD patients.

The favorable effects of EVT on the oxidative status in PAD patients can be attributed to improvements in both arterial flow – reflected by the improvement in the ABI – and perfusion to peripheral tissues. In the present study, the improvement in the ABI was significantly correlated with the delta d-ROM levels. However, the favorable effects of EVT on the oxidative status might also be partly attributed to the improvement in the walking distance. Several studies have reported a correlation between regular physical activity and oxidative stress.[41,42]

In the present study, we also noted a significant correlation between baseline d-ROM and delta d-ROM levels. Thus, the decrease in d-ROM levels was more prominent in patients with a higher baseline d-ROM level. This result suggests that the effects of EVT on oxidative stress in PAD patients might be markedly greater in those with severe atherosclerosis.

We observed that EVT improved the maximum walking distance and relieved leg pain in patients with PAD. EVT might also play an important role in preventing systemic atherosclerotic diseases by reducing the oxidative stress through improvements in peripheral blood flow and walking distance. Therefore, we believe that EVT could not only alleviate leg symptoms but also improve patient prognosis by preventing or delaying systemic atherosclerosis. However, at present, there are no studies indicating that EVT can improve the prognosis of PAD patients, and further studies are required to prove our hypothesis.

This study has certain limitations. As this study focused on patients from a single medical center, the sample studied was comparatively small. Moreover, a longer follow-up period than that used in the present study is required to confirm the influence of oxidative stress on clinical outcomes.

In conclusion, EVT improved the oxidative status in patients with PAD. The effects of EVT were correlated significantly with improvements in the ABI and maximum walking distance values. Furthermore, the effects of EVT were more prominent in patients with a higher oxidative status at baseline.

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