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Kitano, Ikuro

Sugimoto, Takaki

Okada, Masayoshi

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# QUANTITATIVE ASSESSMENT OF PERIPHERAL OCCLUSIVE ARTERIAL DISEASES BY COLOR DUPLEX SONOGRAPHY AND BLOOD ENDOTHELIN LEVEL

Ikuro KITANO, Takaki SUGIMOTO, and Masayoshi OKADA

Second Division, Department of Surgery ,
Kobe University School of Medicine

## INDEXING WORDS

occlusive arterial diseases; color duplex sonography ; blood endothelin level

## SYNOPSIS

To evaluate peripheral occlusive diseases quantitatively, we performed color duplex sonography and measured the blood endothelin (ET-1) level.

***Materials and Method;*** We measured the systolic velocities of the dorsal pedial and the posterior tibial arteries as well as the brachial artery. We also calculated the flow volume, and the ratio of systolic velocities and flow volume of the lower to upper extremity (AVI, AFI ). Furthermore we measured the blood ET-1 level and investigated the relationship between this value and clinical symptoms.

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Authors' names in Japanese: 北野育郎、杉本貴樹、岡田昌義

***Results;*** The value of AVI as well as AFI decreased in the order of Fontaine class I, II, III and IV. In four limbs with a Fontaine class greater than II with a normal ankle pressure index , the values of AVI were low . On the other hand, three limbs with normal values of peak-AVI ($>0.9$) and lower API ($<0.75$) were in Fontaine class I. The value of the ET-1 level was higher in Fontaine class III and IV than in class II, and decreased after revascularization along with improvement of clinical symptoms.

***Conclusions;*** The new AVI and AFI values shoewd a better correlation with clinical symptoms than API. The ET-1 level was significantly higher in Fontaine class III and IV, and showed marked regression after arterial reconstruction.

Thus, the new AVI and AFI values may provide a novel means of identifying patients with the peripheral occlusive diseases, and the measurement of ET-1 level may be potentially useful in identifying the severity of arteriosclerosis.

## INTRODUCTION

Angiography, including intraarterial digital subtraction, is the most accepted standard to evaluate peripheral arterial occlusive disease qualitatively. However, this method is invasive, not repeatable and cannot provide a quantitative evaluation. To evaluate this disease quantitatively, we measured the ratio of velocity and flow volume of the lower to upper extremity by color duplex sonography. Furthermore, many previous studies have confirmed a relationship between endothelin and arteriosclerosis.[8][10][11] However, few studies have examined the relationship between the blood endothelin level (ET-1) and clinical severity due to arteriosclerosis. Thus, we also examined this relationship in this paper.

## MATERIALS AND METHOD

# QUANTITATIVE ASSESSMENT OF ARTERIAL DISEASES

Between July 1996 and July 1998, we examined sixty-eight limbs of 40 patients using color duplex sonography in addition to intraarterial digital subtraction angiography to evaluate peripheral arterial occlusive disease. They consisted of 38 males and 2 females, ranging in age from 21 to 85 years (mean, 67.3 years). Twenty-five limbs were in Fontaine class I, 30 in class II and 13 in class III and IV. Surgical or endovascular intervention was performed for twenty limbs with over Fontaine class II. Fourteen limbs underwent bypass operation, (femoro-popliteal bypass: 10 limbs, femoro-posterior tibial bypass: 1, axillo-femoral bypass: 1, axillo-femoral and femoro-popliteal bypass: 2), and 6 limbs received endovascular intervention (percutaneous transluminal angioplasty : 1, Laser+percutaneous transluminal angioplasty+Stenting: 5). Recordings were obtained with a color-flow Doppler ultrasonic duplex scanner (Toshiba SSA-100) with an examination angle between the Doppler ultrasound beam and the flow jet of 60 degrees or less with a 7.5 MHz linear-array probe. After the patients rested for 10 minutes, we measured the mean and peak systolic velocities (mean, peak SV) of the dorsal pedial artery (DPA) and the posterior tibial artery (PTA), as well as those of the brachial artery (BA). We mesasured the areas of the arteries using gray-scale imaging and calculated the mean and peak flow volume (mean, peak FV). The arteries were examined with the patient in the supine position. Color flow imaging was used to identify the vessel. All arteries were defined in both longitudinal and transverse planes. Velocity determinations were performed at an insonating angle of 60 degrees or less. The mean and peak systolic velocities varied and were affected by individual cardiac output per minute of the patients. In order to eliminate the influence of individual cardiac output, we calculated the ratio of mean, peak SV and FV of the lower to upper extremity (AVI, AFI), and examined the relationships of these values to clinical symptoms and the conventional ankle pressure index (API).

mean AVI=mean SV of DPA or PTA / mean SV of BA

peak AVI=peak SV of DPA or PTA / peak SV of BA

mean AFI=mean FV of DPA or PTA / mean FV of BA peak AFI=peak FV of DPA or PTA / peak FV of BA

Furthermore, we measured the blood ET-1 (endothelium-derived constricting factor: EDCF) level in fourteen limbs of Fontaine class I, 23 limbs of Fontaine class II and 8 limbs of Fontaine class III and IV. Before the operation, 1 week after the operation, and every 6 months thereafter, we measured the blood ET-1 level from venous blood flow in the dorsal vein of the ischemic lower extremity. In this study, blood was sampled from the dorsalis vein since ET-1 is produced in peripheral blood vessels, particularly, capillaries of the ischemic limbs, according to previous reports.[2)12)] To measure the blood ET-1 level, radioimmunoassay using anti-ET-1 serum was employed.

### *Statistical analysis*

Values were expressed as the mean ± standard error. For comparisons between the 3 groups, we used analysis of variance, including Post-Hoc comparisons with Fisher's PLSD. When observations of postoperative changes of the values were carried out, we used the paired Student's t-test. Significance was defined as $p<0.05$.

## RESULTS

### *Relationships between peak AVI and API.*

The peak-AVI was significantly correlated with API, ($R=0.679$, $p<0.05$). However, in four limbs with normal API ($>0.9$) and lower values of peak-AVI ($<0.5$), 3 limbs were in Fontaine class II , and another in Fontaine class III. All of these four limbs showed severe atherosclerotic changes in 3 infrapopliteal vessels with calcification by intraarterial digital subtraction angiogram as well as ultrasound sonogram. On the other hand, three limbs with normal values of peak-AVI ($>0.9$) and lower API ($<0.75$) were in Fontaine class I. These limbs showed well-developed collaterals into the dorsal pedial or the posterior tibial arteries by angiograms (Fig. 1).

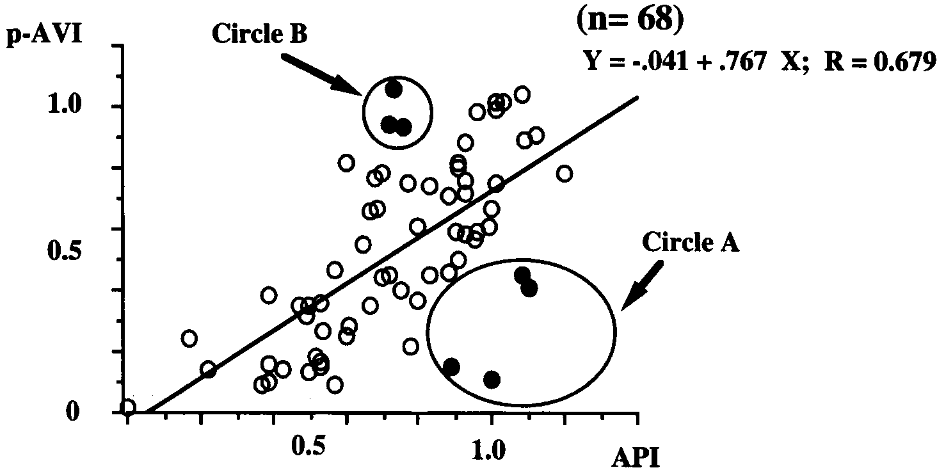


**Fig 1. Relationships between peak AVI and API.**
The peak-AVI was significantly correlated with API, (R=0.679, $p<0.05$). However in four limbs with normal API (>0.9), and lower values of peak-AVI (<0.5) **(Circle A)**, three limbs were in Fontaine class II, and another one in Fontaine class III. On the other hand, three limbs with normal values of peak-AVI (>0.9) and lower API (<0.75) **(Circle B)**, were in Fontaine class I.
peak-AVI; peak ankle velocity index   API; ankle pressure index

***Relationships between AVI, AFI and clinical symptoms***

The values of peak-AVI and mean-AVI showed lower in Fontaine class I ( 0.738 ± 0.043, 0.828±0.051), class II ( 0.477 ±0.049, 0.564±0.048 ), and class III, IV (0.199±0.043, 0.265 ±0.052) in order. The values of peak-AFI and mean-AFI also showed lower in Fontaine class I ( 0.171±0.016, 0.198±0.018), II (0.086± 0.012, 0.108±0.013), and III, IV (0.028± 0.011, 0.045±0.014) in order (Fig. 2).

***Changes of AVI and AFI after revascularization***

The values of peak and mean AVI showed significant improvement after revascularization (0.257 ±0.030→0.699±0.049, 0.354±0.037→0.796±0.061, $p<0.05$). The values of peak and mean AFI also revealed significant improvements (0.038± 0.006→0.160 ±0.017, 0.058 ±0.008→ 0.179±0.061, $p<0.05$) after revascularization (Fig. 3 ).

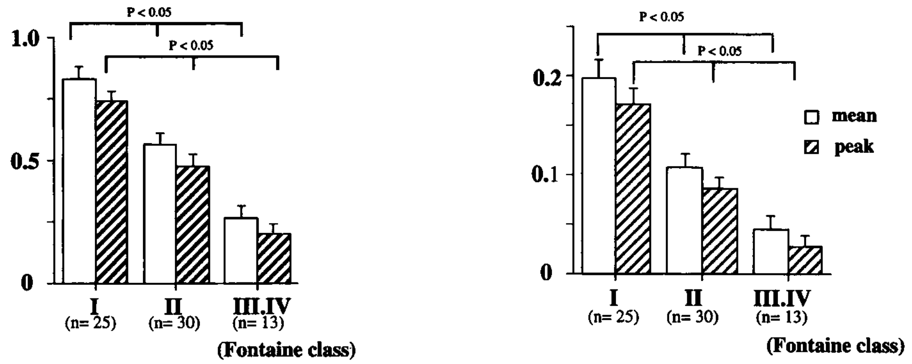


**Fig.2. Relationships between AVI, AFI and clinical symptopms.**
The value of peak-AVI as well as mean-AVI showed significantly lower in Fontaine class I, II, and III, IV in order. The values of peak-AFI and mean-AFI also showed lower in Fontaine class I, II, and III, IV in order.
AVI; ankle velocity index AFI; ankle flow volume index

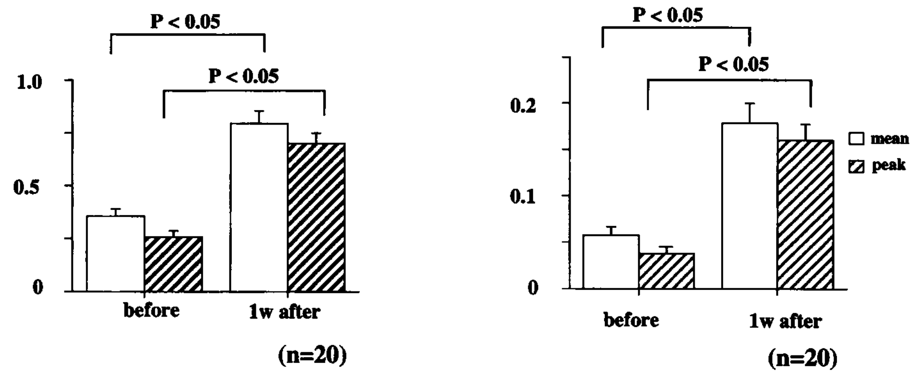


**Fig.3. Changes of AVI and AFI after revascularization.**
Twenty limbs underwent revascularization. After revascularization mean and peak AVI, AFI revealed significant improvements.

***Relationships between blood endothelin (ET-1) level and clinical symptoms***

The ET-1 level was significantly higher in Fontaine class III and IV ( n=8, 3.45 ± 0.23 pg/ml) than in class II (n=23, 2.65 ± 0.16pg/ml). However, there were no significant differences between class I (n=14, 2.66 ± 0.19pg/ml) and class II (Fig. 4 ). All limbs in Fontaine class III and IV showed higher values of blood ET-1 than the normal level (< 2.35pg/ml).

***Changes of serum endotheline level after revascularization***

The ET-1 level showed significant decreases in Fontaine class III and IV limbs 1 week after revascularization and 6 months later, and clinical symptoms also improved to Fontaine class I accordingly (Fig. 5).

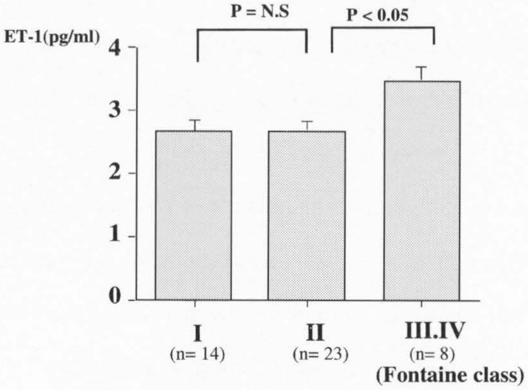


**Fig.4. Relationships between serum endothelin (ET-1) level and clinical symptoms.**
The ET-1 level showed significantly higher in Fontaine class III and IV ( 3.45 ±0.23 pg/ml) than in class II (2.65±0.16pg/ml). However, there were no significant differences between class I and class II .

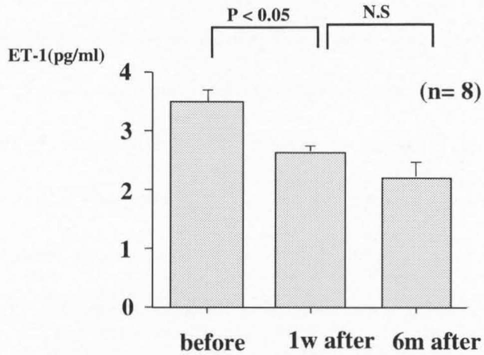


**Fig.5. Changes of serum ET-1 level after revascularization.**
The ET-1 level showed significant decreases in Fontaine class III and IV limbs one week after revascularization, and furthermore six months later. Clinical symptoms also improved to Fontaine class I accordingly.

## DISCUSSION

Angiography, magnetic resonance angiography and duplex scanning in addition to API are useful methods to evaluate the severity of occlusive arterial diseases in the lower limb. The API reflects the pressure of the dorsal pedial and the posterior tibial arteries. However, the API is sometimes higher than that estimated from clinical symptoms and blood flow velocity in patients developing severe arterial sclerosis of the arterial wall with markedly reduced elasticity. On the contrary, the peripheral run off is comparatively preserved even if the API is low in some patients with well-developed collaterals in the peripheral part of the crus. Thus, the API is not correlated with clinical symptoms in some cases. Our study revealed that the AVI was low in patients who showed normal API but were clinically in Fontaine class II or higher. On the other hand, patients showing low API but normal AVI were in Fontaine class I.

Angiography is invasive, not repeatable and can not be used for quantitative evaluation of blood flow although it is necessary to determine the qualitative severity and surgical methods.[3][13] Duplex scanning is non-invasive, repeatable, and can provide quantitative determination of blood flow. However, the velocity and flow volume in the peripheral arteries are not sufficient indices for general evaluation of severity because these indices are influenced by individual heart rate and cardiac output.[15] At present, the indices that are conventionally used include the pulsatile index and resistance index. However, these indices can provide significant differences only in patients with stenosis of 50% or greater, and are often influenced by individual heart function. Therefore, duplex scanning is generally limited to detect the stenotic sites and calculate the stenotic rate from changes of the velocities in the stenotic sites and central and peripheral parts from the sites.[5][15] In this study, we measured mean and peak systolic velocity and flow volume from the waveform the dorsal pedial and the posterior tibial arteries as well as the brachial artery. As well as in calculation of API, the ratios of these values of lower to upper extremity were calculated as mean-AVI, peak-AVI, mean-AFI and peak-AFI. These indices can compensate for the limitations of API caused by being the ratio of pressure as described above. In fact in this study, AVI and AFI were significantly decreased in cases of higher Fontaine classes, and showed a good correlation with clinical symptoms.

The peak-AVI showed the best correlation with API, and the AFI is superior to the others in the evaluation of flow volume itself. However, when stenosis occurs in the artery, the duration of forward flow is prolonged in accordance with reduction in the peak velocity in the peripheral arteries. If stenosis progresses further, forward flow is seen at the diastole as well, showing a waveform similar to that of the vein.[4][16] In addition, calculated values of flow volume itself become rather lower because the inner diameters of the dorsalis pedis and posterior tibial arteries are smaller than that of the brachial artery. Therefore, the standard value of AFI is not 1, differing from those of API and AVI, and some error may occur while measuring the inner diameter. From these perspectives, we consider that the mean-AVI is the most useful index, and that the mean-AVI = 0.4 is the critical point of occlusive arterial diseases because significant ischemic symptoms were found in patient showing 0.4 or less of the mean-AVI.

On the contrary, ET-1, which is present in vascular endothelial cells, is known to have a potential vasoconstrictive effect via ETA receptors on smooth muscles.[1)9)] Facilitation of growth of the vascular inner membrane via ETB receptors has been also clarified.[6)9)14)] Previous studies have shown increased ET-1 levels in the peripheral blood of patients with hypertension, diabetes mellitus and arterial sclerosis.[8)10)11)] Especially in patients with arterial sclerosis, blood ET-1 levels were significantly increased,[7)] and were positively correlated with the number of vascular lesions, according to a report by Lerman *et al.*.[8)] However, there have been no reports examining the relationship between peripheral blood flow and the ET-1 level. In this study, blood was sampled from the dorsalis vein since ET-1 is produced in peripheral blood vessels, particularly, capillaries of the ischemic limbs, according to previous reports.[2)12)] ET-1 levels in the peripheral vein were significantly and abnormally higher in all cases of Fontaine class III and IV than in other classes, while between Fontaine class I and II, there were no significant differences. Thus, blood ET-1 levels reflected the severity of the ischemic limbs particularly in severe cases of Fontaine class III and IV. In all limbs that showed high ET-1 levels and underwent surgical revascularization, the ET-1 levels decreased after surgery and had a tendency to further decrease 6 months after surgery. These results suggested that the elevated ET-1 levels in patients with severe ischemic symptoms were decreased as ischemia subsided after revascularization.

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