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● Original Article ●

A Study of Limb Hemodynamics during Hemodialysis

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Abstract: The study was undertaken to evaluate and analyze the limb hemodynamics of patients with chronic renal failure during hemodialysis, using near-infrared spectroscopy (NIRS). In addition, the study was to test the validity of the hypothesis that ischemia of the limbs takes place during hemodialysis. Fourty-nine patients received hemodialysis at the department of hemodialysis and apheresis of the University of Tokyo Hospital between April 2000 and February 2002. Of them, 6 were excluded due to being rated inappropriate for the study. In the remaining 43 patients, tissue hemoglobin index (THI) and tissue oxygenation index (TOI) of the limbs were measured during hemodialysis, using NIRS. The THI increased in both the calf and the thigh during hemodialysis, while TOI in both the calf and thigh decreased during hemodialysis. With cases complicated by ASO, TOI of the calf rose gradually during hemodialysis. Changes observed in THI and TOI suggest that tissue arterial blood volume increases relatively in the stenosed or obstructed area of the limbs during hemodialysis. In conclusion, NIRS during hemodialysis revealed the possibility of relatively increased tissue arterial blood volume through limb muscle tissue in ASO-accompanied patients who were suspected of limb ischemia. (J Jpn Coll Angiol, 2006, **46:** 217–224)

Key words: limb hemodynamics, hemodialysis, near-infrared spectroscopy (NIRS), saturation, arteriosclerosis obliterans (ASO)

Introduction

A number of patients complain of lower limb pain or tightness during hemodialysis. A possible explanation for these symptoms is that a change in blood pressure and tissue blood volume during hemodialysis alters blood distribution in the body, resulting in limb pain or tightness due to ischemia of the limbs. To date, no papers have yet to conduct an objective evaluation of limb hemodynamics during hemodialysis.

Methods available for the noninvasive and quantitative evaluation of limb hemodynamics include measurement of ankle brachial pressure index (ABPI) using a Doppler blood flow meter, measurement of toe pressure using photoplethysmography, measurement of skin perfusion pressure (SPP), transcutaneous measurement of oxygen tension ($TcPO_2$), scintigraphy, thermography and near-infrared spectroscopy (NIRS). Of these methods, noninvasive NIRS allows the accurate real-time evaluation of hemodynamics in tissue. This method also allows comparison of hemodynamics among different patients and analysis of the time course of hemodynamics in the same patient.[1, 2]

The present study was undertaken to evaluate and analyze the limb hemodynamics of patients with chronic renal failure during hemodialysis, using NIRS, with the goal of testing the validity of the hypothesis that limb ischemia develops during hemodialysis. The study focused on analyzing differences in hemodynamics in relation to the presence/absence

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Table 1 Patients' characteristics

	ASO	ASO-free	p value
No. of patients	14	29	
Sex (male : female)	11 : 3	23 : 6	> 0.9999
Age	63.8 ± 9.72	62.1 ± 12.4	0.6591
Duration after introduction of hemodialysis (month)	64.57 ± 80.32	43.00 ± 78.52	0.2709
Fat thickness (thigh) (mm)	3.72 ± 1.64	4.11 ± 2.69	0.5685
Fat thickness (calf) (mm)	3.76 ± 2.10	3.82 ± 1.84	0.9071
ABPI	0.88 ± 0.59	1.2 ± 0.15	0.0008
Causal disease for CRF			
CGN	3	6	> 0.9299
DM nephropathy	8	13	0.4490
Nephrosclerosis	2	5	> 0.9999
Complication			
DM	9	15	0.4370
Hypertension	12	23	0.7019
Ischemic heart disease	2	4	> 0.9999
Cerebral vessel disease	1	3	> 0.9999
Malignancy	2	10	0.2785
Pain of lower limb during hemodialysis	3	0	0.0295

ABPI: ankle brachial pressure index, CRF: chronic renal failure, CGN: chronic glomerulonephritis, DM: diabetes mellitus

of obstruction of the limb arteries.

Patients and methods

Of the patients who received hemodialysis at the Department of Hemodialysis and Apheresis of the University of Tokyo Hospital between April 2000 and February 2002, 49 patients gave written informed consent to participate in the study. The 49 lower limbs of these 49 patients (36 limbs of 36 males, 13 limbs of 13 females) were studied. Six patients (6 limbs examined) were excluded from the analysis for the following reasons: 1) hemodynamics failed to stabilize during NIRS, necessitating discontinuation of the hemodialysis sessions; or 2) a reduction in blood pressure or oxygen saturation required for oxygen therapy during hemodialysis. The underlying diseases responsible for renal failure in the 43 patients analyzed were chronic glomerulonephritis (9 cases), diabetic nephropathy (21 cases), nephrosclerosis (7 cases), IgA nephropathy (1 case), lupus nephritis (1 case), Leriche syndrome (bilateral renal artery obstruction) (1 case), neurogenic bladder (1 case), vesicoureteral reflux (1 case) and unknown (1 case). In 14 (32.6%) of the 43 cases, renal failure was complicated by arteriosclerosis obliterans (ASO). A diagnosis of ASO was made in cases where at least one of the following signs was noted:

1) ABPI below 0.9[3]
2) Rated as type 1 or 2 by treadmill NIRS, involving a 5-minute walk for 190 m at an inclination of 12 degrees and at a maximum speed of 2.4 km/hr[4-6]
3) Angiographic finding of atherosclerotic stenosis or obstruction of the arteries

Table 1 summarizes characteristics of the patients studied.

There was no significant difference between the ASO group and the ASO-free group in terms of the number of cases, male-to-female ratio, age, fat thickness, duration after introduction of hemodialysis, underlying disease responsible for chronic renal failure, or presence/absence of complication by diabetes mellitus, hypertension, ischemic heart disease,

cerebrovascular disease or malignant tumor. The incidence of limb pain was significantly higher in the ASO group ($p = 0.0295$). The API value was significantly lower in the ASO group ($p = 0.0008$). As for duration after introduction of hemodialysis, there was no significant difference between the cases with and without ASO ($p = 0.2709$).

NIRS

NIRS allows the noninvasive measurement of changes in muscular or brain tissue oxygen metabolism and hemodynamics. The basic principle of NIRS is described elsewhere.[2] NIRS was performed using an NIRO300 (Hamamatsu Photonics KK). The parameters analyzed were tissue hemoglobin index (THI) and tissue oxygenation index (TOI).[7] THI represents absolute total hemoglobin level (cHb, μmol/l) if a site measured is flat and intensity of tissue scattering is close to an average level. The present study, however, analyzed THI as a relative value of total Hb level, since the conditions under which THI accurately represents cHb vary among different individuals or different sites of measurement.

NIRS parameters and evaluation of tissue blood flow

(1) THI

With hemoglobin in the blood retained within the blood vessels, and without leaking out of blood vessels, it is peasible to evaluate tissue blood volume by measuring tissue hemoglobin level.[8, 9] Tissue blood volume is maximal in the veins. When measuring tissue blood volume through the limbs, we raised the limbs of the subjects to avoid influence from the veins. Furthermore, after water was removed during hemodialysis, the tissue blood volume rate measured was corrected for the volume of water removed. In the present study, tissue blood volume was estimated from THI measured with an NIRO300 primarily in the limb-raising position.

(2) TOI

TOI indicates the percentage of oxygenated hemoglobin against total tissue hemoglobin. This parameter is expected to vary depending on the ratio of venous volume to arterial volume. In the present study, arterial oxygen tension was estimated from changes in oxygen saturation, while minimizing the influence from the veins by raising the limbs.

Procedures for NIRS

The protocol shown below was used for NIRS.

1) The limb to be measured is kept still in a supine position.
2) The NIRS probe is attached to the thigh (lateral great muscle) and the calf (gastrocnemius muscle).
3) The subject remains bed rest for one minute. In a horizontal position, THI and TOI are measured.
4) The limb to be measured is raised with a special foot stand (about 20 cm each side), followed by THI and TOI measurement.
5) Steps 3) and 4) are repeated four times (for less than 15 minutes before a session of hemodialysis, for less than 15 minutes after the start of hemodialysis, for less than 15 minutes before the end of hemodialysis and for less than 15 minutes after hemodialysis). At the same points in time, blood pressure (BP) was measured in a noninvasive manner, accompanied by measurement of heart rate (HR) and peripheral oxygen saturation (SpO_2) at the fingertip on the side contralateral to the shunted side. THI and TOI were measured for several minutes (sampling time 0.5 seconds) at each point of measurement, and the data from a total of 120 points, allowing stable 60-second continued measurement, were averaged to yield values of THI and TOI in a given subject. For statistical analysis of the data, the Mann-Whitney U-test and the Wilcoxon signed rank test were employed.

Furthermore, the fat thickness of the probe-attached site was measured three times by the supersonic wave devise (Logiq 500, GE Yokokawa Medical System Co.) and these average were calculated in the thigh and calf. Resting API was measured.

Results

Fat thickness of the thigh or calf showed no significant difference regardless of sex or the presence/absence of ASO.

(1) Changes in THI

1) Time course of THI

THI of the thigh is denoted as THI-T. THI of the calf is indicated by THI-C. THI-T and THI-C measured before, after the start, before the end and after the end of hemodialy-

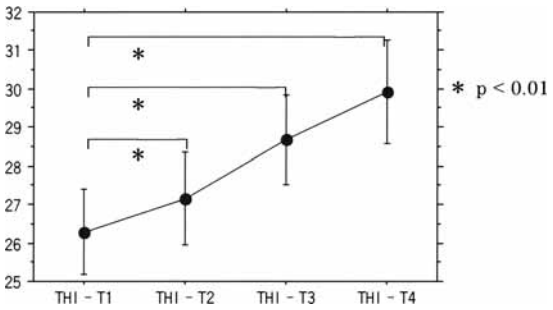

Figure 1 Time course of THI-T.
k × μmol/l (k: an unknown constant)

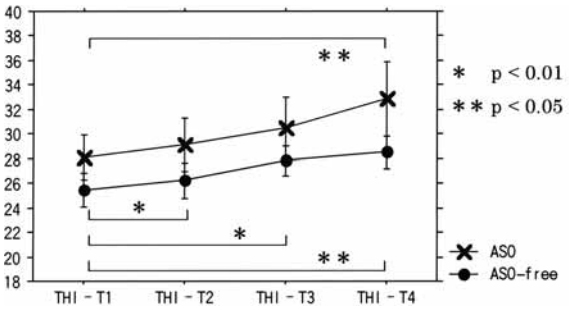

Figure 3 Time course of THI-T in the ASO group and the ASO-free group.
k × μmol/l (k: an unknown constant)

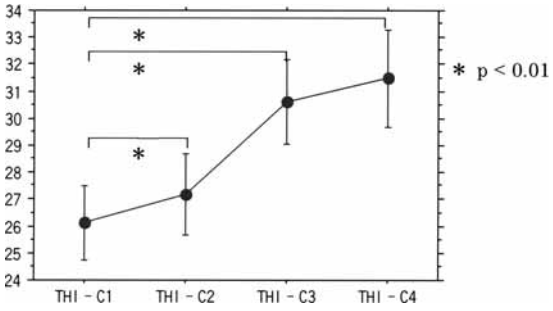

Figure 2 Time course of THI-C.
k × μmol/l (k: an unknown constant)

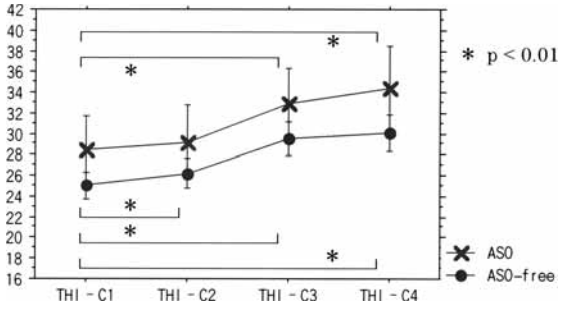

Figure 4 Time course of THI-C in the ASO group and the ASO-free group.
k × μmol/l (k: an unknown constant)

sis are called THI-T1, THI-T2, THI-T3, THI-T4, THI-C1, THI-C2, THI-C3 and THI-C4, respectively. **Figs. 1** and **2** graphically represent the time course of THI-T and THI-C, respectively.

The analysis of the time course of THI-T revealed that THI-T2, THI-T3 and THI-T4 were markedly higher than THI-T1 ($p = 0.0011, 0.0066, < 0.0001$, respectively). In analysis of THI-C, we noted that THI-C2, THI-C3 and THI-C4 were markedly higher than THI-C1 ($p = 0.0018, < 0.0001, < 0.0001$, respectively).

Figs. 3 and **4** show the time course of THI for each of the ASO group and the ASO-free group.

In the ASO group, THI-T2 and THI-T3 tended to be higher than THI-T1 although the difference was statistically in significant ($p = 0.1981, 0.4703$). THI-T4 was significantly higher than THI-T1 in the ASO group ($p = 0.0303$). In the ASO-free group, THI-T2, THI-T3 and THI-T4 were significantly higher than THI-T1 ($p = 0.007, 0.0067, 0.0005$).

In the ASO group, THI-C2 was higher than THI-C1 although the difference was in significant ($p = 0.2455$). THI-C3 and THI-C4 were significantly higher than THI-C1 ($p = 0.0010, 0.0012$). In the ASO-free group, THI-C2, THI-C3 and THI-C4 were significantly higher than THI-C1 ($p = 0.0024, < 0.0001, < 0.0001$).

There was no significant difference in THI-T between the ASO group and the ASO-free group at any of the four points of measurement ($p = 0.4523, 0.3924, 0.5511, 0.3924$). THI-C also showed no significant inter-group difference at any of the four points of measurement ($p = 0.4523, 0.6595, 05511, 0.5511$).

2) Changes in THI ratio

Since THI indicates a relative value of total hemoglobin level, we analyzed percentage changes in this parameter. During hemodialysis, tissue volume decreases as water is being removed. Therefore, when comparing hemoglobin levels, adjustment to changes in tissue volume is indispens-

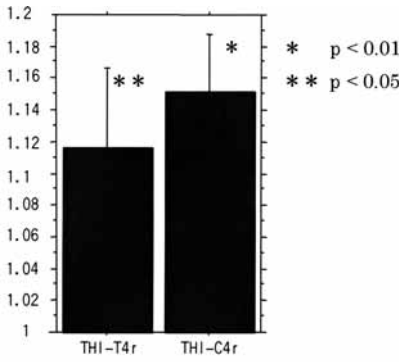

Figure 5 Changes in THI-T4r and THI-C4r.

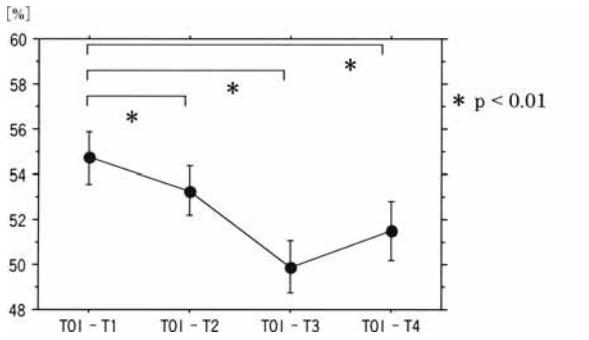

Figure 7 Time course of TOI-T during hemodialysis.

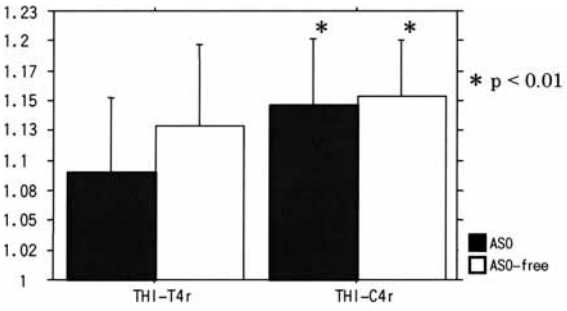

Figure 6 Changes in THI-T4r and THI-C4r in the ASO group and the ASO-free group.

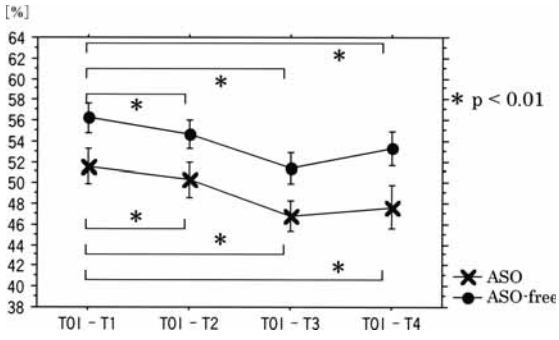

Figure 8 Time course of TOI-T during hemodialysis in the ASO group and the ASO-free group.

able. A serous hemoglobin level was examined at the hemodialysis start and end, described as Hb-1 and Hb-2 respectively. The parameter THI-T4/THI-T1 and THI-C4/THI-C1 are revised as follows:

$$\text{THI-T4r} = \text{THI-T4/THI-T1} \times \text{Hb-1/Hb-2}$$

$$\text{THI-C4r} = \text{THI-C4/THI-C1} \times \text{Hb-1/Hb-2}$$

THI-T4r and THI-C4r are expressed in **Fig. 5**. The graph of THI-T4r and THI-C4r in ASO group in **Fig. 6** in comparison with ASO-free group.

As shown in **Fig. 5**, THI-T4r rose significantly ($p = 0.0413$). When analyzed separately in the ASO group and the ASO-free group, this parameter showed no significant change in the ASO group ($p = 0.3003$) and in the ASO-free group ($p = 0.0817$). There was no significant difference in THI-T4r between the two groups ($p = 0.8764$).

Fig. 5 additionally shows that THI-C4r rose significantly ($p = 0.0001$). As shown in **Fig. 6**, this parameter rose significantly in both groups (ASO group: $p = 0.0092$, ASO-free group: $p = 0.0034$). There was, however, no significant inter-group difference in this parameter ($p = 0.8357$).

(2) Changes in TOI (Time course of TOI)

TOI of the thigh is denoted as TOI-T. TOI of the calf is indicated by TOI-C. TOI-T and TOI-C measured before, after the start, before the end and after the end of hemodialysis are called TOI-T1, TOI-T2, TOI-T3, TOI-T4, TOI-C1, TOI-C2, TOI-C3 and TOI-C4, respectively. **Figs. 7–10** graphically represent the time course of TOI-T and TOI-C and their analysis in relation to the presence/absence of ASO.

The analysis of the time course of TOI-T revealed that TOI-T2, TOI-T3 and TOI-T4 were notably lower than TOI-T1 ($p < 0.0001$). When the time course of TOI-T was analyzed in relation to the presence/absence of ASO (**Fig. 8**), there was no significant difference between the ASO group and the ASO-free group in any of TOI-T1, TOI-T2, TOI-T3 and TOI-T4 ($p = 0.0780, 0.0657, 0.0585, 0.0696$). In both groups,

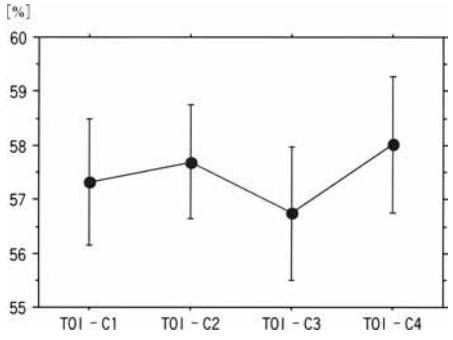

Figure 9 Time course of TOI-C during hemodialysis.

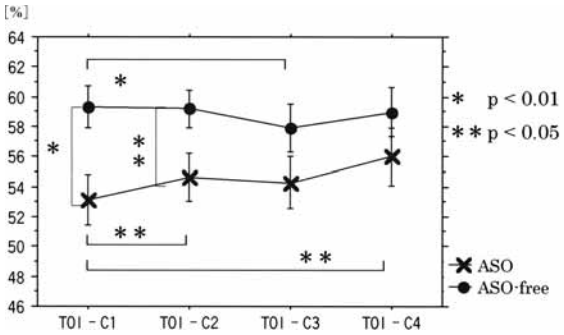

Figure 10 Time course of TOI-C during hemodialysis in the ASO group and the ASO-free group.

TOI-T2, TOI-T3 and TOI-T4 were significantly lower than TOI-T1 (ASO group: p = 0.0186, 0.0010, 0.0029, ASO-free group: p = 0.0004, < 0.0001, 0.0029).

TOI-C1 and TOI-C2 were significantly lower in the ASO group than in the ASO-free group (p = 0.0082, 0.0258), while there was no significant inter-group difference in TOI-C3 or TOI-C4 (p = 0.1467, 0.2232) (**Fig. 10**). In the ASO group, TOI-C rose immediately after the start of hemodialysis (p = 0.0413), remained almost unchanged thereafter (p = 0.7299) and rose again after the end of hemodialysis (p = 0.0355) (**Fig. 10**). In the ASO-free group, TOI-C2 and TOI-C4 did not differ significantly from TOI-C1 (p = 0.6576, 0.3359) while TOI-C3 was significantly lower than TOI-C1 (p = 0.0159) (**Fig. 10**).

When patients with ASO were subdivided into two groups; with and without suprainguinal occlusive lesion, TOI-T4 decreased statistically in each group (p = 0.0464 and p = 0.0003 respectively).

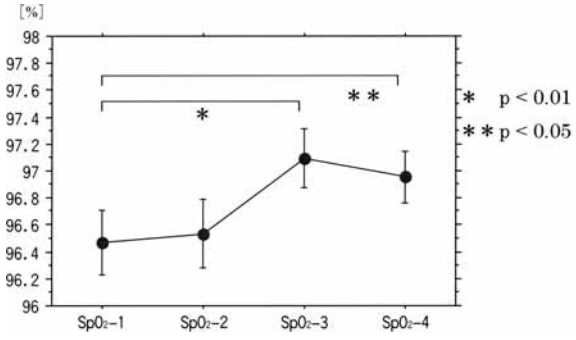

Figure 11 Time course of SpO_2 during hemodialysis.

(3) Changes in SpO_2

SpO_2 measured before, after the start, before the end and after the end of hemodialysis are called SpO_2-1, SpO_2-2, SpO_2-3 and SpO_2-4, respectively. **Fig. 11** graphically represents the time course of SpO_2.

SpO_2-4, measured approximately during maximum water removal, was significantly higher than SpO_2-1 (p = 0.0202).

(4) Changes in TOI and THI in patients developing limb pain during hemodialysis

During the present study, 3 patients developed limb pain (all from the ASO group). TOI measurement was resumed immediately after the onset of pain. TOI-T, TOI-C, THI-T and THI-C measured immediately after the onset of pain are called TOI-T', TOI-C', THI-T' and THI-C', respectively. **Table 2** summarizes the characteristics of these patients.

But no sign of reduced tissue blood volume (e.g., reduction in THI or TOI) was noted in these patients.

Discussion

(1) Changes in THI and THI ratio of the thigh and calf

Since hemoglobin is found only in the blood vessels, measurement of tissue hemoglobin level is expected to allow the evaluation of tissue blood volume. Yamamoto et al. and Talpahewa et al. describe that THI is expressed as a parameter of cerebral blood volume.[8, 9] THI is a relative value and it can vary depending on the shape, structure and optical properties of the sites measured. For this reason, we analyzed percentage changes in THI in the present study. During hemodialysis, water is removed, reducing the tissue volume.

Table 2 Characteristics of patients who developed limb pain

	Patient 1	Patient 2	Patient 3
Sex	Male	Male	Male
Age	72	54	55
Fontaine classification	IV	IV	II
TOI-T1[%]	60.3	52.8	43.8
TOI-T' [%]	57.9	48.6	41.1
TOI-C1[%]	60.3	56.6	43.2
TOI-C' [%]	61.8	57.4	55.0
THI-T1[k × μmol/l]	25.8	23.6	39.4
THI-T' [k × μmol/l]	28.8	21.2	47.1
THI-C1[k × μmol/l]	17.8	24.0	61.1
THI-C' [k × μmol/l]	19.5	24.0	65.7

k: unknown constant

Therefore, the THI measured was adjusted to the amount of water removed before comparison. The adjusted THI ratio showed a similar time course in both the thigh and the calf. In both regions, this parameter rose significantly during hemodialysis. This change was observed to a similar degree in both the ASO group and the ASO-free group, especially in the calf. These results suggest that limb tissue blood volume is possible to increase during hemodialysis.[10]

(2) Changes in TOI

Despite improved blood oxygenation during hemodialysis, both TOI-T and TOI-C tended to decrease over time during hemodialysis. It is particularly noteworthy that in the ASO group, TOI rose gradually from the start to the end of hemodialysis. That is, although TOI tended to decrease in areas without arterial stenosis and obstruction, it rose in areas showing arterial stenosis or obstruction. The finding of reduced tissue oxygen saturation despite elevation in tissue hemoglobin level and elevation in arterial and shunt blood oxygen saturation suggests that tissue venous blood volume is relatively increased more than tissue arterial blood volume. This means that hemodialysis can elevate tissue venous blood volume in areas without stenosis and obstruction. It is also estimated that the relative increase in tissue arterial blood volume is greater than that of tissue venous blood volume in stenosed or obstructed areas. On the basis of these findings, only stenosed or obstructed areas are possible to show a relative increase in arterial blood flow during hemodialysis.

(3) Changes in limb tissue blood volume

The difference observed in tissue blood volume between the thigh and the calf suggests that the change in tissue blood volume during hemodialysis is attributable to local accommodative reactions rather than systemic reactions. It seems likely that factors involved in the regulation of tissue blood volume gather in the ischemic areas to suppress ischemia and increase tissue blood volume. This phenomenon may involve the following factors. First, the formation of interleukin-1 (IL-1) increases during hemodialysis.[11] IL-1 stimulates the formation of prostacyclin (PGI_2) by vascular endothelial cells. PGI_2 induces vasodilation and suppresses platelet aggregation. Tissue blood volume is probably increased by this factor. Furthermore, IL-1 also stimulates the formation of prostaglandin E_2 (PGE_2). PGE_2 also suppress local platelet aggregation. This factor also seems to increase tissue blood volume. Moreover, it has been reported that inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) increase during hemodialysis.[12-14] It seems probable that these cytokines improve local tissue blood volume during hemodialysis. However, all of these previous reports pertained to elevation of blood levels of these factors occurring as systemic reactions and none of them specifically dealt with local reactions. Our literature search did not reveal any previous papers addressing local cytokine reactions involved in the regulation of tissue blood volume. It is therefore desirable that additional studies are conducted on this topic.

(4) Causes of limb pain during hemodialysis

In the present study, three patients developed limb pain when NIRS was being performed during hemodialysis. In all these cases, it was possible to resume TOI measurement soon after the onset of pain. No change such as decrease in TOI was seen in these patients after resumption of measurement. If these findings are combined, it seems unlikely that the limb pain observed during hemodialysis was attributable to ischemia. It is empirically known that the intravenous administration of hypertonic saline or high-sodium dialysis is useful in alleviating limb pain during hemodialysis. There-

fore, loss of electrolyte balance (loss of sodium, hyponatremia) during hemodialysis may be one possible factor responsible for the pain. Other pain-causing factors can be an elevated K/Ca ratio or Pi level in cerebrospinal fluid, reduced myocyte pH, delayed urea nitrogen removal. Because the number of patients who complained of limb pain during hemodialysis was insufficient in the present study, additional studies involving more patients are required. Recent and continued advances in the management of hemodialysis patients contribute to reduced incidence of hypoxemia during hemodialysis, suggesting that limb pain is unlikely caused by limb ischemia during hemodialysis.

Conclusion

It is clinically known that hemodialysis patients sometimes complain of limb pain. We hypothesized that this pain is attributable to limb ischemia during hemodialysis. The present study was designed to test the validity of this hypothesis. NIRS during hemodialysis revealed the possibility of relatively increased arterial tissue blood volume through limb muscle tissue in ASO-accompanied patients who were suspected of limb ischemia.

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