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Evaluation of Changes in Oxygenation by Near Infrared Spectroscopy during Direct Hemoperfusion with Polymyxin B Immobilized Fibers

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Near-infrared spectroscopy (NIRS) is a continuous, non-invasive measurement to relatively evaluate tissue oxygen delivery and cellular aerobic metabolism. In the present study, to more understand the therapeutic efficacy of direct hemoperfusion with polymixin B-immobilized fibers (PMX-DHP), we investigated changes of tissue oxygenation by using NIRS and compared before and after PMX-DHP treatment. We measured oxygenated hemoglobin (Oxy-Hb), deoxygenated hemoglobin (Deoxy-Hb), total hemoglobin (Total Hb) and cytochrome a,a_3 (Cyt a,a_3) at forehead and forearm using NIRS. Data obtained by using a Swan-Ganz catheter was used to derive systemic $\dot{V}O_2$ (oxygen consumption), $\dot{D}O_2$ (oxygen delivery), O_2EI (oxygen extraction index), SVRI (systemic vascular resistance index) and SvO_2 (mixed venous oxygen saturation). At forearm, Cyt a,a_3 significantly increased after PMX-DHP ($p<0.05$). At forehead, there were no changes of Cyt a,a_3 ($p=0.39$) between before and after PMX-DHP. And there were no significant changes in $\dot{V}O_2$, $\dot{D}O_2$, O_2EI, SVRI, SvO_2, blood lactate concentration, base excess and IL-6. After PMX-DHP treatment, Oxy-Hb, Deoxy-Hb, Total Hb and Cyt a,a_3 increased at the forearm. But at forehead, Cyt a,a_3 was unchanged. This result suggests PMX-DHP could increase blood volume and tissue oxygen metabolism in skeletal muscles in septic shock.

Key words: sepsis, polymyxin B, cytochrome a,a_3, near-infrared spectroscopy, intensive care unit

Introduction

The endotoxin absorption therapy, which is the direct hemoperfusion with polymyxin B-immobilized fibers (PMX-DHP) has been often used for the patients with endotoxemia or gram negative infection in Japan[1)~3)]. Recently, the first multi-center randomized controlled trial of PMX-DHP for severe sepsis or septic shock has been done in Europe. In that study, Vincent et al reported PMX-DHP improved hemodynamic status and oxygen delivery but did not change blood endotoxin levels and the prognosis[4)]. We also observed the improvement of hemodynamic status by PMX-DHP treatment in sepsis although blood endotoxin concentration did not change[5)]. Some study shows the contribution of PMX-DHP treatment to improve the hemodynamic status in sepsis[6)~9)]. However the conflicting results have been shown about the prognosis, endotoxin or cytokine levels in blood by PMX-DHP treatment[10)~17)]. Thus the mechanisms of PMX-DHP for sepsis have not been elucidated and further studies are required[18)].

In sepsis, the impairment of systemic oxygenation is well known because of the imbalance of oxygen supply and demand[19)]. Clinically, these parameters have been observed as changes in oxygen delivery ($\dot{D}O_2$) and oxygen consumption ($\dot{V}O_2$), mixed venous oxygen saturation (SvO_2) measured through a Swan-Ganz catheter. Raised blood lactate concentration during septic shock has been often viewed

as evidence of tissue hypoxia[20]. Cellular dysfunction in sepsis may be caused not by inadequate tissue perfusion but rather by impaired mitochondrial respiration ("cytopathic hypoxia")[21]. Therefore, clinicians also would like a way to, evaluate oxygen metabolism in the cellular level are required.

The efficacy of near-infrared spectroscopy (NIRS) has been reported for the relative evaluation of tissue oxygenation, which measures the redox status of cytochrome a,a_3 (Cyt a,a_3)[22]. The redox status of Cyt a,a_3 reflects oxygen supply at the cellular level and NIRS enables measurements continuously relative oxygenated hemoglobin (Oxy-Hb) concentration, relative deoxygenated Hb (Deoxy-Hb) concentration (oxygen delivery), and the redox status of Cyt a,a_3 (oxygen metabolism) from the analysis of absorption of different wave length signals by tissue. Since Jobsis reported regarding spectroscopic measurements of Cyt a,a_3 redox state in 1977, NIRS has been used for measurement of oxygen metabolism[23]. Initially, this non-invasive method was used to measure the cerebral-oxygenation during cardiac surgery[24)25]. However, recently, the clinical utility of NIRS is recognizing to evaluate tissue oxygenation[22)26)~30].

We hypothesized that tissue oxygen metabolism could be improved during PMX-DHP treatment in sepsis. The present study shows the changes of tissue oxygenation by using NIRS during PMX-DHP in patients with endotoxic shock.

Patients and Methods

Patients

Patients with a diagnosis of septic shock according to the criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference and with proven or suspected infection of gram-negative bacteria and requiring vasoactive agents were enrolled in the study[31]. The patients who required red blood cell transfusions during this protocol were excluded. PMX-DHP procedure was started when patients admitted to the intensive care unit (ICU). All patients had a Swan-Ganz catheter inserted.

Sedation and neuromuscular blockade

Midazolam (Astellas Pharma Inc., Tokyo Japan; 0.03-0.12 mg/kg/h) or propofol (AstraZeneca PLC., London England; 1.5-3.0 mg/kg/h) were administered along with pancuronium bromide (Organon Inc., Oss Netherlands; 0.02-0.03 mg/kg/h). All cases were maintained in a resting position to avoid any spontaneous movements throughout this protocol.

PMX-DHP

Blood access was obtained by insertion of a 12 Fr triple lumen catheter (Arrow International Inc., Reading, PA USA) into the femoral vein using Seldinger's method. PMX-DHP (Toraymyxin®, Toray Medical Co., Ltd.,Tokyo Japan) was performed for 2 h at a blood flow rate of 100 ml/min by a direct hemoperfusion method as described. An anticoagulant, nafamostat mesilate (Torii Pharmaceutical Co., Ltd.,Tokyo Japan), was administered continuously at 20-40 mg/h[2)32].

Near-infrared spectroscopy (NIRS)

NIRS measures Oxy-Hb, Deoxy-Hb, and the oxidation status of Cyt a,a_3 in mitochondria through the skin using near-infrared light (700-1,000 nm wavelength). The tissues of the body contain substances that absorb or scatter light. The light absorption characteristics of some components, such as hemoglobin and Cyt a,a_3, are changed by oxygen concentration. Although there are other substances in the body whose absorbance changes with changes in oxygen concentration, they do not absorb near-infrared light at the wavelength used. To measure changes in the concentration of these components, the absorbance due to other substances that are constant if off set in the baseline and does not influence the specific absorption of these substances. Thus, changes in concentration of Hb and Cyt a,a_3 can be calculated by measuring these "light out". When light of wavelength λ_1 is illuminated through a transparent sample, light of intensity I passes through.

Then, concentration C is obtained by the following formula the Beer-Lambert Law (formula a):

$$C = 1/(\varepsilon d) \cdot \log (I/I_0) \qquad (a)$$

Where I_0: illuminated light intensity, ε: absorption coefficient, and d: light pathlength. This formula can be used only with homogeneous systems in which light is not scattered, but it can be used approxi-

mately with inhomogeneous systems such as the body accordingly to formula b:

$$C = 1/(\varepsilon L) \cdot \log (I/I_0) + X \qquad (b)$$

Where X is the light intensity that is not detected due to light scattering and cannot be measured generally. However, since this loss of light intensity is constant, the concentration change from time t to t_0 can be obtained as $\Delta C = C(t) - C(t_0)$. Thus, our data are shown as Δ changes, and not absolute values. L is the light pathlength, which is the distance of the light path from the illumination point to the detection point in tissue[33)34)].

The NIRO-300 instrument (Hamamatsu Photonics K.K., Hamamatsu Japan) used in the present study is equipped with two probes, which enable measurements simultaneously from two different sites. The probes were attached to the forehead (HEAD), and a site 5 cm distal to the elbow joint on the palmar side of the radial bone in the right forearm (Forearm). The probes were fixed with tape and cloth, under which measurements were made protected from light. The actual light pathlength is the distance between the point sending light and receiving light, d, multiplied by the differential pathlength factor, B ($L = B \cdot d$). The differential pathlength factor is known to change depending on the tissue type and age[33)34)]. The distance between the point sending light and receiving light is 4.0 cm with the NIRO-300. The actual light pathlength is 16 cm, 4 times the distance, at the forearm and 24.0 cm, 6 times the distance, at the forehead. NIRS was performed and recorded from 30 min before starting of PMX-DHP until 30 min after the completion of PMX-DHP. Data of Oxy-Hb, Deoxy-Hb, Total Hb and Cyt a,a_3 were obtained continuously every 30 sec for 10 min, 10 min before starting PMX-DHP (PRE) and 5 min after the completion of PMX-DHP (POST) (Fig. 1).

Data obtained using the Swan-Ganz catheter

With a pulmonary artery catheter (model No. 774 HF75: Edwards Lifesciences Co., Ltd., Irvine, CA USA) inserted in the right internal jugular vein or left or right subclavian vein, oxygen consumption ($\dot{V}O_2$), oxygen delivery ($\dot{D}O_2$), oxygen extraction index (O_2EI), systemic vascular resistance index (SVRI) and mixed venous oxygen saturation (SvO_2) were examined by using an Edwards CEDV monitor (Edwards Lifesciences Co., Ltd.) before and after PMX-DHP simultaneously with NIRS measurements.

Serum lactate concentration, blood base excess, and serum interleukin (IL)-6 concentration. These parameters were measured immediately before PMX-DHP and 15 min after completion of the treatment. Using serum from 1.5 mL blood, lactate concentration was measured using an enzymatic method, following protein removal by centrifugation at 3,000 rpm. Base excess was measured in arterial blood using a Rapid Lab Model 806 blood gas analyzer (Bayer Medical Ltd., Leverkusen Germany). Serum IL-6 concentration was measured by chemiluminescent enzyme immunoassay (FujiRebio Inc., Tokyo Japan).

Statistical analyses

All data are shown as means ± SEM, except when stated otherwise. When distributed normally, all hemodynamic parameters and blood data were compared by paired t test and when not distributed normally, all data measured by NIRS were compared by the Wilcoxon signed ranks test. Statistical significance was declared for p values less than 0.05. All analyses were performed using JMP version 5.0.1. J (SAS Institute Inc. Cary, NC USA).

Result

Eighteen septic shock patients, 12 males and 6 females, were enrolled in this study. Mean age was 64 ± 14 years old and APACHE II score on admission to ICU was 22 ± 5. Surgical procedure was performed to 89% of patients. Gram-negative bacteria were detected from blood culture in 8 patients. The mortality rate in 28 days was 33% (Table 1).

1. NIRS during PMX-DHP

Figure 1 shows practical record of NIRS. Oxy-Hb, Deoxy-Hb and Total Hb at the forearm were significantly increased after PMX-DHP compared with before PMX-DHP (7.67 ± 1.62 vs 4.61 ± 1.39 $\Delta\mu$mol/L, $p < 0.05$; 2.66 ± 0.90 vs 1.51 ± 0.60 $\Delta\mu$mol/L, $p < 0.05$; 10.3 ± 2.16 vs 6.12 ± 1.71 $\Delta\mu$mol/L, $p < 0.01$; respectively) (Fig. 2). At the forehead Deoxy-Hb and Total Hb were significantly decreased after PMX-

Table 1 Characteristics of patients treated with PMX-DHP

Patient (No.)	Age (year)	Gender	APACHE II score	Diagnosis	Surgical treatment	Result of blood culture	Outcome
1	36	Female	15	Necrotizing esophagitis	Bi-thoracic D	Negative	Died
2	65	Male	34	*Escherichia coli* pneumonia	NS	E.C	Died
3	69	Female	15	Perforation of rectum	C and D	Negative	Survived
4	58	Male	20	Perforation of sigmoid colon	C and D	Negative	Survived
5	54	Male	21	Intestinal necrosis and perforation	SBR and D	B.F	Survived
6	57	Male	19	Multiple liver abscesses	NS	B.F	Survived
7	67	Male	17	Perforation of rectum	C and D	Negative	Survived
8	73	Female	16	Obstructive colitis	C and D	Negative	Died
9	36	Male	18	Idiopathic esophageal rupture	Thoracic D	Negative	Survived
10	73	Female	25	AOSC	Biliary D	Negative	Survived
11	47	Male	21	Bowel obstruction	SBR and D	B.F	Died
12	88	Male	24	Bowel obstruction	SBR and D	Negative	Died
13	63	Female	28	Perforation of sigmoid colon	Sigmoid resection and C and D	B.F	Survived
14	80	Female	22	Perforation of small intestine	SBR and I and D	C.F and K.O	Survived
15	76	Male	18	Perforation of stomach	Gastrectomy and D	Negative	Survived
16	66	Male	22	SMA thrombosis	Subtotal bowel resection	Negative	Died
17	72	Male	29	AOSC	Biliary D	K.P	Survived
18	65	Male	28	AOSC	Biliary D	K.O	Survived

The breakdown of whole patients during study period. Male: 12, Female: 6, n = 18. AOSC: acute obstructive suppurative cholangitis, SMA: superior mesenteric artery, D: drainage, NS: no surgery, C: colostomy, SBR: small bowel resection, I: ileostomy, E.C: *Escherichia coli*, B.F: *Bacteroides fragilis*, C.F: *Citrobacter freundii*, K.O: *Klebsiella oxytoca*, K.P: *Klebsiella pneumoniae*.

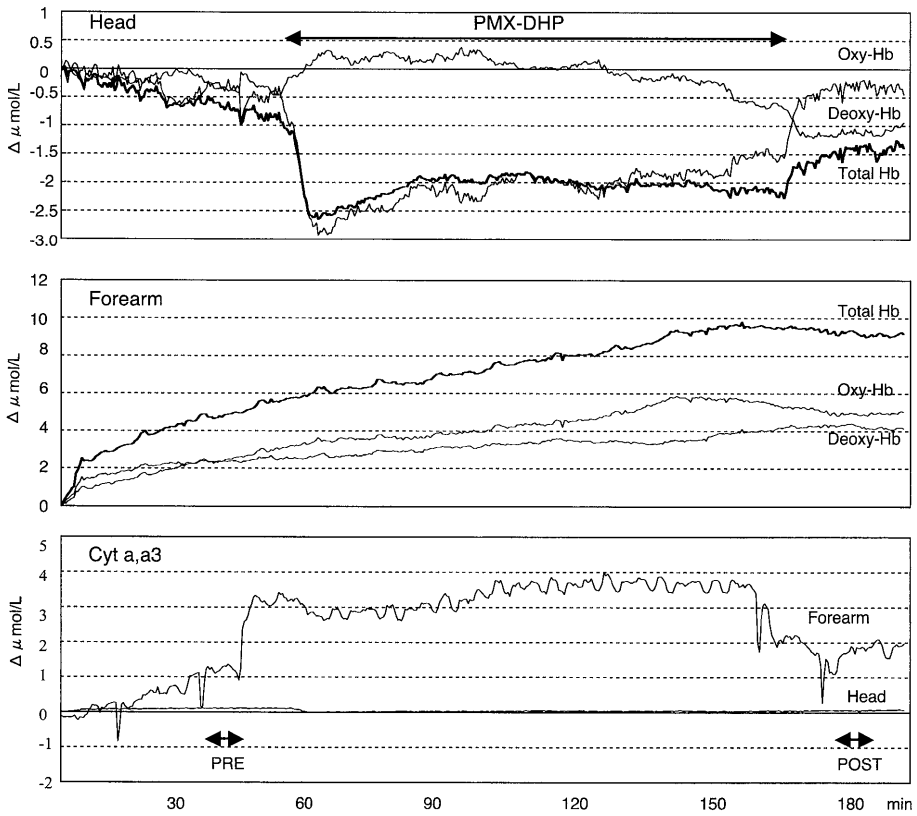

Fig. 1 The practical NIRS records under PMX-DHP treatment in patient 58 year old, male HEAD is the probe attached on the skin at the forehead. FOREARM is the probe attached on the skin at 5 cm distal from the elbow joint to the palmar on the right radial bone. PRE is 10 min just before PMX-DHP. POST is 5 min after the completion of PMX-DHP. The measurements last for 10 min.

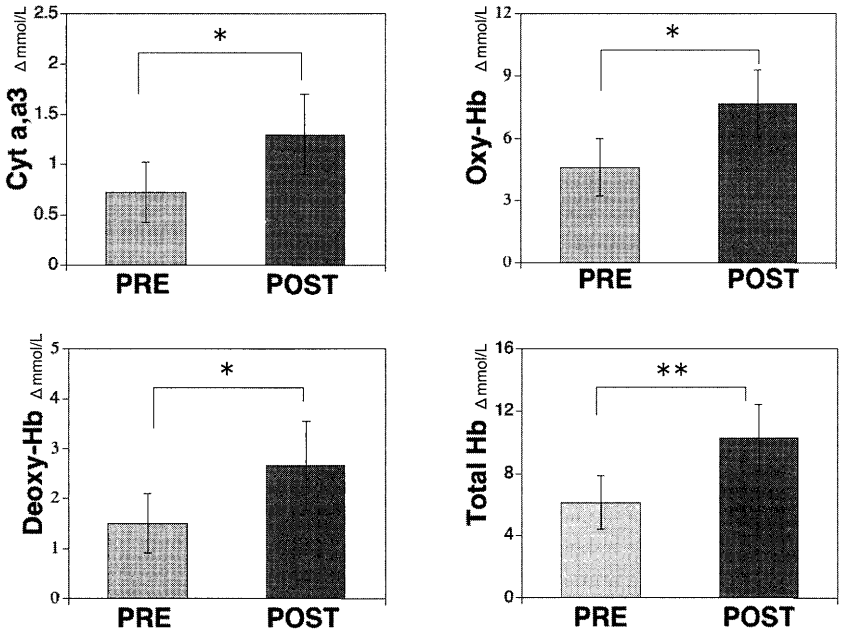

Fig. 2 The changes of Oxy-Hb, Deoxy-Hb, Total Hb and Cyt a,a_3 at forearm
PRE (gray bar) is 10 min before PMX-DHP starting. POST (black bar) is 5 min after the completion of PMX-DHP. The measurements last for 10 min.
Data are means ± SEM, n=18. * $p < 0.05$, ** $p < 0.01$.

DHP compared to before, but Oxy-Hb did not change between after and before PMX-DHP (-1.15 ± 0.28 vs -0.24 ± 0.16 Δμmol/L, $p<0.01$; -1.80 ± 0.57 vs 0.39 ± 0.65 Δμmol/L, $p<0.05$, -0.65 ± 0.56 vs 0.63 ± 0.6 Δμmol/L, $p=0.0569$ respectively) (Fig. 3). Cyt a,a_3 of forearm was significantly increased after PMX-DHP compared to before (1.30 ± 0.41 vs 0.72 ± 0.30 Δμmol/L, $p<0.05$), but there was no change of Cyt a,a_3 at forehead between after and before PMX-DHP (0.01 ± 0.07 vs 0.04 ± 0.05 Δμmol/L, $p=0.39$) (Figs. 2, 3).

2. Hemodynamic parameters and blood data

Mean arterial pressure (MAP) was increased after PMX-DHP compared with before PMX-DHP. $\dot{V}O_2$, $\dot{D}O_2$, O_2EI, SVRI and SvO_2 were no significant changes during PMX-DHP. Serum lactate concentration, base excess and serum IL-6 concentration were also unchanged between before and after PMX-DHP. Blood hemoglobin concentration and hematocrit were statistically decreased after PMX-DHP (Table 2).

Discussion

Since 1994 when PMX-DHP was approved as a therapy for patients with endotoxic shock under national health insurance system in Japan, PMX-DHP has been commonly used for those patients. Therapeutic efficacy of PMX-DHP has been claimed to associate with increases in blood pressure by causing to directly adsorb endotoxin in blood[3)11)35)]. However some study showed there were no changes in endotoxin or cytokine levels in blood after PMX-DHP and PMX-DHP did not relate to patient's outcome[4)]. Recently, some data suggest that PMX-DHP increases blood pressure because this treatment removes of endogenous anandamide and 2-AG which are compounds produced by macrophages and platelets cause hypotension[36)~38)]. Other study shows PMX-DHP decreases blood lactate concentration[1)] and improves pulmonary oxygenation[2)11)]. Thus, a consensus on the therapeutic efficacy of PMX-DHP has not been reached and mechanism still has not been determined. Indeed, it may be difficult to prove the mechanism of PMX-DHP, since it is a short period hemoperfusion for only 2 h procedure.

In the present study, we evaluated therapeutic effect of PMX-DHP by analyzing the status of tissue oxygenation at the cellular level by using NIRS. Our result shows there are no changes in global body

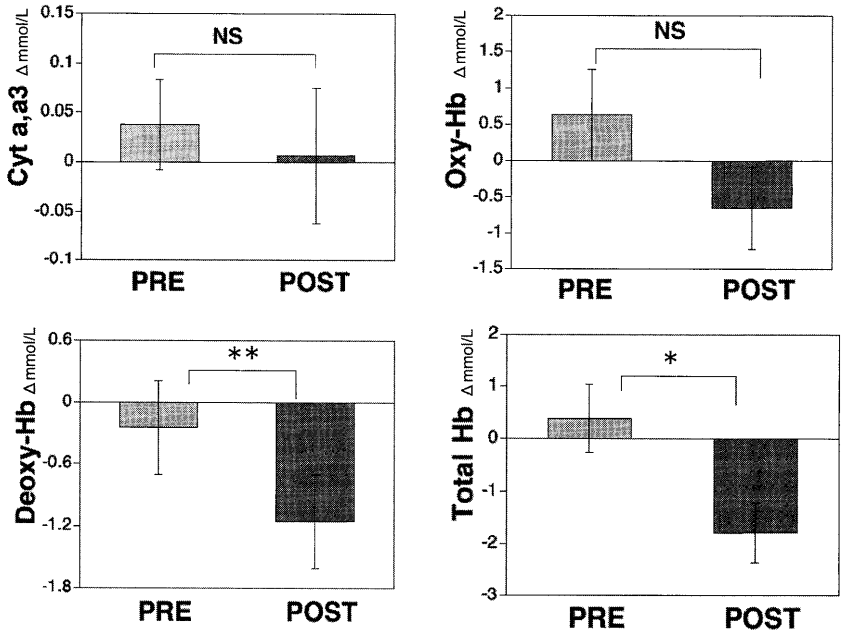

Fig. 3 The changes of Oxy-Hb, Deoxy-Hb, Total Hb and Cyt a,a_3 at forehead
PRE (gray bar) is 10 min before PMX-DHP starting. POST (black bar) is 5 min after the completion of PMX-DHP. The measurements last for 10 min.
Data are means ± SEM, n=18. * $p < 0.05$, ** $p < 0.01$, NS: not significant.

Table 2 Whole body hemodynamic parameters, blood parameters and mean blood pressure, IL-6 level

Variable	PRE	POST	p value
MAP	81.4 ± 16.6	88.8 ± 16.0	0.031 *
$\dot{V}O_2$	200 ± 14.6	212 ± 17.2	0.29
$\dot{D}O_2$	876 ± 72.1	902 ± 72.2	0.55
O_2EI	23.0 ± 1.82	23.6 ± 1.63	0.67
SVRI	1,640 ± 155	1,670 ± 162	0.70
SvO_2	75.0 ± 1.93	74.3 ± 1.81	0.54
Lactate	11.1 ± 3.2	10.8 ± 3.3	0.61
BE	− 1.93 ± 0.90	− 1.06 ± 0.93	0.19
Hb	11.2 ± 0.43	10.8 ± 0.45	0.015 *
Hct	32.8 ± 1.24	31.8 ± 1.32	0.029 *
IL-6	14,400 ± 7,750	12,700 ± 8,330	0.54

PRE: before PMX-DHP, POST: after PMX-DHP. Data are mean ± SEM. p values were analyzed by paired t test. *$p < 0.05$, n = 18. $\dot{V}O_2$: oxygen consumption (mL/min/m^2), $\dot{D}O_2$: oxygen delivery (mL/min/m^2), O_2EI: oxygen extraction index, SVRI: systemic vascular resistance index (dynes·s/cm^5·m^2), SvO_2: mixed venous oxygen saturation (%), lactate: (mg/dL), BE: base excess (mmol/L), Hb: hemoglobin of whole body (g/dL), Hct: hematocrit of whole body (%), MAP: mean blood pressure (mmHg), IL-6: interleukin-6 (pg/mL).

oxygenation and hemodynamics, increase in Cyt a,a_3, Oxy-Hb, Deoxy-Hb and Total Hb at forearm site and decrease in Deoxy-Hb and Total Hb at forehead site, while Oxy-Hb and Cyt a,a_3 do not change after PMX-DHP. Blood lactate, base excess or IL-6 also do not change. Hence, in this study, there are no major effects of PMX-DHP on body metabolism, but it is possible to ameliorate tissue oxygenation.

In previous studies, it was shown that the redox status of Cyt a,a_3 present in the mitochondrial inner membrane, which was measured by NIRS, correlates with oxygen metabolism at the cellular level[22)39)~41)]. Using a hyperdynamic sepsis model of gram-negative bacteria induced by intravenous injection of coliforms in primates, Simonson et al, continuously measured $\dot{D}O_2$ and $\dot{V}O_2$ through a pulmonary artery catheter and Cyt a,a_3 by NIRS after fluid resuscitation[39)]. The results showed that $\dot{D}O_2$ and $\dot{V}O_2$ changed slightly after 24 h while Cyt a,a_3 decreased markedly in 2 to 3 h as measured by NIRS. In addition, Simonson et al showed that mitochondrial function in biopsies of intact muscle were correlated with Cyt a,a_3 redox state. Therefore, they concluded that measurement of Cyt a,a_3 by NIRS enabled measurement of a rapid response in several hours and thus permitted evaluation of mitochondrial function. Forget et al, using a septic

model induced by injection of lipopolysaccharide (LPS) in piglets, continuously measured $\dot{D}O_2$, $\dot{V}O_2$ and Cyt a,a_3 by NIRS in the hindleg while controlling blood flow by isolating the femoral artery and vein of the hindleg[38]. They showed $\dot{D}O_2$ and $\dot{V}O_2$ did not change, but Cyt a,a_3 significantly decreased as well. In our study, Cyt a,a_3 increased significantly in the forearm muscles after PMX-DHP, we could conclude that PMX-DHP improves mitochondrial oxygen metabolism.

Hemoglobin measured by NIRS reflects the mean Hb concentration in tissues, but it does not show the concentration in blood. Oxy-Hb increases when (a) blood oxygen saturation increases, (b) arterial blood volume increases when there is an increase in blood pressure, (c) oxygen carried by Hb increases, and (d) tissue oxygen consumption decreases. Deoxy-Hb level changes according to oxygen saturation and circulation. Oxy-Hb and Deoxy-Hb change disproportionately upon any decrease in oxygen saturation, venous occlusion, or flow to tissue of blood with a low oxygen saturation, whereas Oxy-Hb decreases and Deoxy-Hb increases upon a decrease in oxygen saturation. By NIRS, blood volume in tissues is obtained as Total Hb (Oxy-Hb + Deoxy-Hb). When the blood volume is unchanged, Oxy-Hb and Deoxy-Hb change in opposite directions, showing no change in Total Hb. When there are any difference in changes of Oxy-Hb and Deoxy-Hb or both, it indicates the change in blood volume[33)34)]. Schaefer et al measured tissue hemoglobin by NIRS in septic model of mice, they showed Total Hb, Oxy-Hb significantly decreased[41)]. We observed Total Hb in the forearm significantly increased, and both of Oxy-Hb and Deoxy-Hb increased as well after PMX-DHP. In addition, whole blood Hb and Hct were significantly decreased after PMX-DHP. From those results, blood volume increase in the forearm, although decreasing whole blood Hb decreases. Therefore there is a possibility to improve in the redistribution of blood by PMX-DHP.

LPS caused collapse of the blood-brain barrier and influx of granulocytes into brain tissues[42)]. We expected Cyt a,a_3, would be increased by PMX-DHP, as seen in the forearm muscle. However, the results in the forehead were different from those in the forearm. Cyt a,a_3 did not show any change in the frontal lobe at the forehead even in the presence of changes in blood volume such as depletion or infusion of blood for PMX-DHP, unlike in the forearm skeletal muscle. Schaefer et al reported that cerebral Cyt a,a_3 measured by NIRS did not change significantly after LPS administration in mice[43)]. These results may suggest that brain tissues are protected by mechanisms such as autoregulation and the brain-blood barrier[44)]. Thus, mitochondrial oxygen metabolism seems to be maintained in the frontal lobe in sepsis.

In our results of measurement of cerebral blood volume, all Oxy-Hb, Deoxy-Hb, and Total Hb decreased after PMX-DHP. Some studies suggested that cerebral blood volume decreased in sepsis, resulting in cerebral hypoperfusion[45)46)]. These data in sepsis suggested that Deoxy-Hb-rich venous blood increased due to maintenance of oxygen consumption, and Oxy-Hb-rich arterial blood decreased and the increase in Total Hb. Therefore, PMX-DHP may alter the redistribution of cerebral blood volume in sepsis.

The present study does not show how PMX-DHP intervenes in the process leading to cellular hypoxia from tissue hypoperfusion in the oxygen metabolism defect associated with sepsis. However, the results show that PMX-DHP ameliorates the mitochondrial oxygen metabolism in skeletal muscle, and that during PMX-DHP a distinct change in blood distribution occurs in the skeletal muscle and in the brain.

This study has some limitations. First, since this is not a controlled, randomized study, a control group is lacking. Practically, it is quite hard to perform the controlled study such as this study by using simple dialysis or plasma exchange as a control group and unify other treatments for septic shock. Therefore, we compare the results between before and after PMX-DHP procedure and analyzed by paired two groups. Second, PMX-DHP is an extra corporeal technique which may induce blood and foreign surface interaction with complement activa-

tion, or leucocyte and platelet changes. These phenomena may affect the results. However, there were no changes of leucocyte or platelet counts, no adverse events happened during this study. Third, after the completion of PMX-DHP, the priming volume which is blood volume in the PMX-DHP circuit outside of the body space may influence the results. We use no hemoglobin containing fluid to prime the circuit with around 230 ml. Nevertheless it could dilute blood and hemoglobin levels, blood volume and Cyt a,a_3 improved in the skeletal muscle.

Conclusions

Oxygenation in peripheral tissues was analyzed using near-infrared spectroscopy, and systemic oxygenation was examined using a Swan-Ganz catheter and compared between before and after PMX-DHP treatment in patients with septic shock. PMX-DHP increased blood volume in skeletal muscle of forearm and improved tissue oxygen metabolism at the cellular level as seen by elevated oxygen metabolism through the mitochondrial electron transfer system. A significant decrease in deoxy-Hb was observed in the frontal lobe at the forehead after PMX-DHP, suggesting an improvement in the redistribution of blood volume. The mitochondrial electron transfer system was maintained in a steady state. There was no change in indices of systemic oxygenation by PMX-DHP. Our results demonstrate PMX-DHP treatment might have the efficacy in tissue oxygenation.

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PMX-DHP 治療前後における近赤外線分光法による組織酸素代謝の変化と評価

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PMX-DHP（direct hemoperfusion with polymyxin B immobilized fiber）は1994年にエンドトキシン吸着療法として日本で認可された治療法であり，現在敗血症症例を中心に広く臨床応用されているが，その臨床的有効性の評価および機序については今も議論のあるところである．筆者らは当センターでPMX-DHPを施行した敗血症症例に対し，近赤外線法（NIRS）を用いて測定可能なcytochrome a,a_3（Cyt a,a_3），酸化ヘモグロビン（Oxy-Hb），還元型ヘモグロビン（Deoxy-Hb），総ヘモグロビン（Total Hb）をPMX-DHP前後で比較することにより，細胞レベルでの組織酸素代謝と血液量の再分布の変化を検討した．対象は東京女子医科大学救命救急センター集中治療室に入室し，PMX-DHPを施行した18症例である．近赤外線装置は前額部，前腕部の2ヵ所に装着し，PMX-DHPを中心に約3時間連続して計測した．また，全身の組織酸素代謝の指標としてSwan-Ganz catheterを使い $\dot{V}O_2$（oxygen consumption），$\dot{D}O_2$（oxygen delivery），O_2EI（oxygen extraction index），SVRI（systemic vascular resistance index），SvO_2（mixed venous oxygen saturation）を測定し，血液検査からはblood lactate concentration, base excess，IL-6を測定した．前腕部の近赤外線法による結果はPMX-DHP前後でCyt a,a_3（$p<0.05$），Oxy-Hb（$p<0.01$），Deoxy-Hb（$p<0.05$），Total Hb（$p<0.01$），すべてに有意差をもって増加した．前額部の前頭葉の近赤外線法による結果は，PMX-DHP前後でCyt a,a_3, Oxy-Hbに変化はなく，Deoxy-Hb（$p<0.01$），Total Hb（$p<0.01$）は，有意差をもって減少した．また，$\dot{V}O_2$，$\dot{D}O_2$，O_2EI，SVRI，SvO_2，blood lactate concentration，base excess，IL-6はPMX-DHPの前後での有意差は認めなかった．結論としてPMX-DHPにより全身の組織酸素代謝の指標に変化を認めなかった．しかし近赤外線法による測定結果は前腕骨格筋での血液量は増加し，さらにミトコンドリア内における電子伝達系の酸素代謝は亢進した．また前頭葉の血液量の分布はPMX-DHPにより改善された．これらの結果はPMX-DHPの有効性を示唆していると考えられた．