Figure 5 shows the experimental circuit which consists of an integrated oxygenator with the CFP (n = 4), a reservoir, the TS410 flow meter (Transonic Systems Inc.), and a BF41 water bath (Yamato Scientific CO., Tokyo, Japan). The index artificial lungs used αCUBE 6000 (Dainippon Ink & Chemicals Co.). The oxygenator and the original model were connected to the roller blood pump Mera HAD101 (Senko Medical Instrument Mfg., Tokyo, Japan). The experiment used bovine blood with a hematocrit of 35%. The blood reservoir was placed in a temperature controlled bath at 37°C. Standard bovine venous blood (O_2 saturation, 65 ± 5%; hemoglobin, 12 g/dl; and partial pressure of carbon dioxide, 45 ± 5 mm Hg) was supplied to the inlet to evaluate O_2 and CO_2 transfer rates. Gas exchange performance was evaluated at blood flow rates of 1, 3, and 4 l/min, with blood and gas flow ratios set at 1. O_2 and CO_2 transfer rates were estimated from the blood gas analysis data. O_2 and CO_2 transfer rates were calculated using the following formulas:

$$O_2\text{content} = (\text{Hb} \times 1.34 \times SO_2)/100 + PO_2 \times 0.003$$

$$O_2 \text{ transfer rate} = (CaO_2 - CvO_2) \times Q$$

$$\text{Total } CO_2 = HCO_3^- + 0.03 \times PCO_2$$

$$CO_2 \text{ transfer rate} = 22.3 \times (tCO_2v - tCO_2a)$$

where Hb is the hemoglobin, PO_2 is the oxygen partial pressure, CaO_2 is the arterial oxygen content, CvO_2 is the venous oxygen content, Q is the blood flow rate, HCO_3- is the plasma bicarbonate ion concentration, PCO_2 is the CO_2 partial pressure, tCO_2v is the venous total CO_2, and tCO_2a is the arterial total CO_2. Blood gas samples were analyzed using the gas analyzer Ciba Corning 248 (Bayer Medical Inc., Tokyo, Japan). Values are expressed as mean ± SD.

Results

The relationship between flow rate and pressure head in the CFP at different motor speeds is illustrated in **Figure 6**. The maximum flow rate of the CFP was 5.38 l/min at 3000 rpm when the pump head was 142 mm Hg.

Computational fluid dynamics (CFD) analysis results are shown in **Figure 7**, and **Table 2** shows a comparison of the uniformity of the blood flow at the hollow fiber membrane part. The standard deviation of the blood flow of the original design at the hollow fiber membrane part was 6.99e-5. The standard deviation of the blood flow for design 1 was 7.80e-6; for design 2, 1.17e-5; and for design 3, 3.42e-5. Compared to the original design as the standard, the uniformity of blood velocity was improved by 88.8% in design 1, by 83.3% in design 2, and by 51.1% in design 3.

The effect of the uniformity of the blood velocity at the hollow fiber membrane part on oxygenator performance was evaluated by gas exchange performance in an *in vitro* experiment. The O_2 and CO_2 transfer rates are shown in **Figure 8** and **Figure 9**. The O_2 and the CO_2 gas transfer performance of the original design were 211 ml/min and 116 ml/min (V/Q = 1), respectively, at a blood flow rate of 4 l/min. With design 1, the O_2 and the CO_2 gas transfer rates were 255 ml/min and 157 ml/min, respectively. The O_2 and CO_2 transfer rates with designs 1, 2, and 3 were higher than in the original design. Overall, when the blood flow rate was 4 l/min, O_2 transfer rates were increased by 20%, and CO_2 transfer rates were increased by 35% in design 1 as compared with the original oxygenator.

At the high flow rate, designs 1, 2, and 3 achieved a higher gas exchange performance than the original oxygenator using a 3/8-inch port. However, no differences in gas exchange performance were found between designs at the low flow rate. The average outlet PO2 of the original design was 531 ± 16 mm Hg at a blood flow rate of 1 l/min. The average outlet PO2 for design 1 was 541 ± 16mmHg; for design 2, 555 ± 19 mm Hg; and for design 3, 555 ± 13mmHg at the same flow rate.

Table 1. Analysis and Boundary Conditions

Porosity of the hollow fiber membrane	0.6
Blood contact surface condition	Nonslip
Outlet flow condition	Free from pressure
Inlet flow rate	3 l/min
Gravitation force	From outlet to inlet
Fluid type	Newtonian
Viscosity of blood	0.0033 Pa·s
Density of blood	1060 kg/m 3

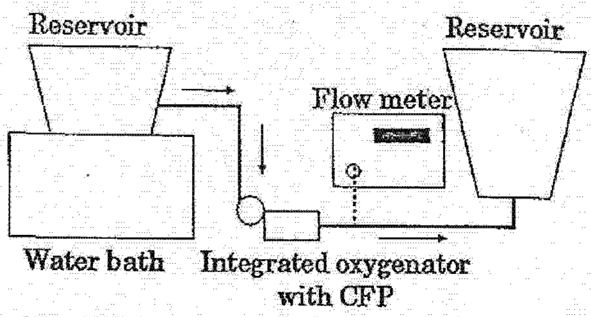

Figure 5. The measurement circuit of gas exchange performance. Gas exchange performance was evaluated using the single path method. The experiment used bovine blood maintained at a temperature of 37°C.

Discussion

The performance requirements of an artificial implantable lung include having a low resistance, achieving adequate gas transfer performance, being nonthrombogenic, and having a

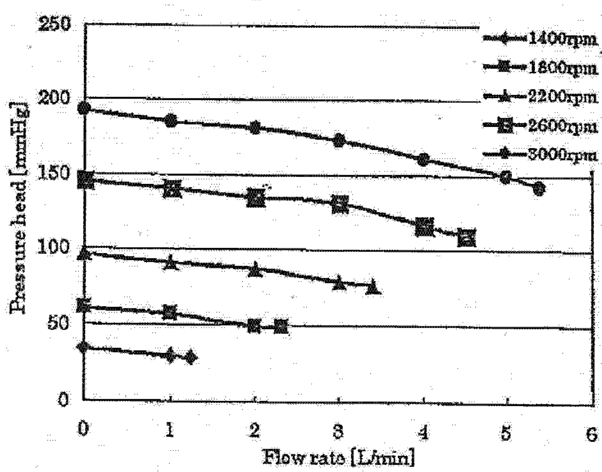

Figure 6. As shown in the graph of pump performance, the CFP generated 5.38 l/min at 3000 rpm when the pump head was 142 mm Hg.

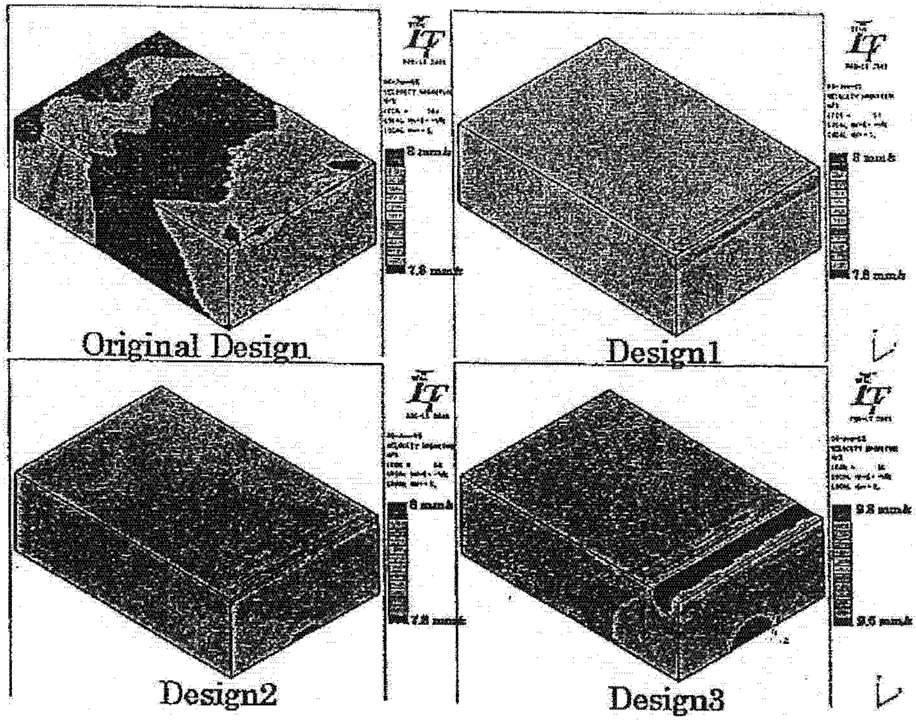

Figure 7. Results of CFD analysis. Shown is the blood velocity at the hollow fiber membrane part.

compact size. Much research has been conducted to improve these performance problems in order to achieve clinical applicability of the artificial implantable lung. Because an integrated oxygenator uses a blood pump, oxygenator resistance that might cause cardiac failure is of no concern. We evaluated the effects of various changes on integrated oxygenator performance by using a combination of CFD analysis and *in vitro* experiments.

Overall, the standard deviation of the blood flow at the hollow fiber membrane part was low with the improved oxygenator models; design 1 had the lowest standard deviation, followed by design 2 and then design 3. One can surmise that the membrane surface area would be used effectively, because the low standard deviation value indicates uniform flow at the hollow fiber membrane part. O_2 and CO_2 transfer rates indicated high gas exchange performance, with design 1 having the highest performance, followed by design 2 and then design 3. From these results, it can be deduced that uniform blood flow in the hollow fiber membrane part influences gas exchange performance. Thus, uniform blood flow can be used as a design parameter for the oxygenator. We compared the gas transfer relationship between the port inflow oxygenator and the wide inflow oxygenator. The blood was fully saturated with any inlet design, because the bundle is overdesigned for a low flow rate. Therefore, at low flow, there is very little difference in the gas exchange performance between the port inflow and the wide inflow. However, the difference between the performances of the oxygenators increased at a high flow rate. When the oxygenator with the port inflow was used, a high flow rate caused channeling and decreased the efficiency of the hollow fiber membrane. Therefore, gas exchange performance was reduced. However, use of the wide inflow oxygenator avoided channeling because the CFP produced a wide uniform flow to the oxygenator. Therefore, the oxygenator used the membrane surface area effectively to achieve a high gas exchange performance. Compared with design 1, design 3 had nonuniform flow and low gas exchange performance. The space between the inlet housing and the hollow fiber membrane was small in design 3. Therefore, channeling was

Table 2. Comparison of Results

	Standard Deviation	Improvement Rate (%)
Original design	6.99e-5	—
Design 1	7.80e-6	88.8
Design 2	1.17e-5	83.3
Design 3	3.42e-5	51.1

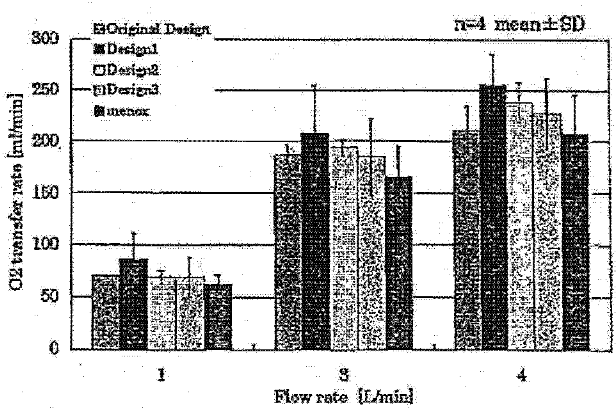

Figure 8. Relationship between O_2 transfer rate and flow rate. O_2 transfer rate of the design 1 was 255 ml/min (V/Q = 1) at a blood flow rate 4 l/min.

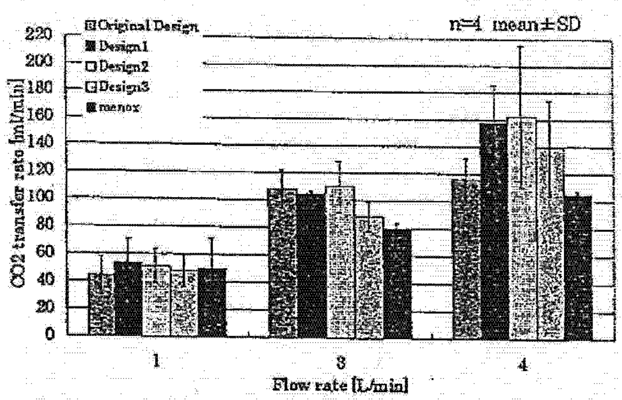

Figure 9. Relationship between CO_2 transfer rate and flow rate. CO_2 transfer rate of the design 1 was 157 ml/min (V/Q = 1) at a blood flow rate 4 l/min.

caused in the hollow fiber membrane part, and gas exchange performance was reduced, because the membrane surface area could not be used effectively. In design 1, kinetic energy was effectively converted to pressure energy, because there is a large space between the inlet housing and the hollow fiber membrane, and the membrane surface area could be used effectively. However, design 1 needed a big priming volume because of the large space. We are planning further studies of integrated oxygenator size, thrombogenicity in the oxygenator, and gas exchange performance.

Conclusion

The result of our experiments suggests that a CFP, which produces a wide uniform flow to the oxygenator, increases the efficiency of the hollow fiber membrane part. We think that this device can be used as an implantable pump oxygenator.

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EFFECTS OF ORAL BERAPROST SODIUM, A PROSTAGLANDIN I_2 ANALOGUE, ON ENDOTHELIUM DEPENDENT VASODILATATION IN THE FOREARM OF PATIENTS WITH CORONARY ARTERY DISEASE

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SUMMARY

1. Previous clinical studies with prostaglandin I_2 (PGI_2) analogue beraprost sodium suggested the potential effects on protection of cardiovascular events in patients with peripheral artery disease. Although the mechanism is not well known, experimental studies have shown protective effects of endothelial cells. This study was designed to examine the effects of beraprost sodium on vascular endothelial function in the forearm of patients with coronary artery disease.

2. Beraprost sodium (120 μg/day) was orally administered to 14 coronary artery disease patients for 4 weeks and then stopped for 4 weeks. Eleven control patients did not receive beraprost sodium treatment. Reactive hyperemia was induced in the forearm, endothelium-dependent vasodilatation was assessed by plethysmography, and urinary 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) was measured at baseline, 4 weeks and 8 weeks.

3. Both groups had similar reactive hyperemic responses at baseline. In the control group, reactive hyperemic response and urinary 8-iso-$PGF_{2\alpha}$ remained unchanged for 8 weeks. In the beraprost group, maximum forearm blood flow increased significantly ($P = 0.01$) after 4 weeks of treatment and returned to baseline at 8 weeks. Duration of hyperemia increased significantly ($P = 0.003$) after 4 weeks, and remained greater than baseline at 8 weeks ($P = 0.02$). Urinary 8-iso-$PGF_{2\alpha}$ decreased significantly ($P = 0.03$) after 4 weeks, and tended to be lower at 8 weeks ($P = 0.07$). Changes in reactive hyperemia correlated weakly but significantly with changes in 8-iso-$PGF_{2\alpha}$ ($P < 0.001$).

4. Beraprost sodium decreased oxidative stress and improved forearm endothelium-dependent vasodilatation in coronary artery disease patients. The favorable effects on vascular endothelium could potentially lead to a decrease in vascular events.

Key words: 8-iso-prostaglandin $F_{2\alpha}$, beraprost sodium, prostaglandin I_2, reactive hyperemia.

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INTRODUCTION

Prostaglandin I_2 (PGI_2), which is synthesised in vascular endothelial and smooth muscle cells after appropriate stimulation by specific agents, shows antiplatelet action[1] and vasodilating action.[2] In addition, PGI_2 acts in concert with nitric oxide, ectonucleotidase and other endothelial molecules to maintain vascular homeostasis and vasoprotection.[3] Beraprost sodium is a stable and orally active PGI_2 analogue and it has antiplatelet and vasodilating properties. Beraprost sodium has been widely used for treatment of pulmonary hypertension and atherosclerotic peripheral arterial disease. The treatment effects with beraprost sodium have been well known in pulmonary hypertension.[4–6] In contrast, there are conflicting results showing that beraprost sodium as an effective[7] or ineffective[8] treatment to improve symptoms of intermittent claudication in patients with peripheral arterial disease. However, these previous studies suggested the potential benefit in cardiovascular events. If beraprost sodium has a protective effect on cardiovascular events, it may improve vascular endothelial function as one of the mechanisms. The favourable effects of beraprost sodium on vascular endothelial function have been reported in experimental *in vivo* studies.[9,10] However, human study regarding the effects of beraprost sodium on vascular endothelial function has not been fully documented.

The present study investigated the ability of beraprost sodium to improve endothelium-dependent vasodilatation in the forearm vessels of patients with endothelial dysfunction. Furthermore, the present study was also designed to examine the effects of discontinuation of treatment with beraprost sodium, because we have experienced some cases that show improvement of symptoms in patients with peripheral artery disease after cessation of treatment with beraprost sodium.

METHODS

Study population and design

The study was performed prospectively in 30 patients with coronary artery disease. Patients were randomly assigned to either a beraprost group, treated with beraprost sodium, or a control group, treated without beraprost sodium. Beraprost sodium (120 μg/day) was orally administered to 15 patients for 4 weeks, followed by 4 weeks without beraprost sodium. The other 14 age- and gender-matched patients were followed but not treated with beraprost sodium. All other medications were continued throughout the course of the study in all the patients and all drugs including beraprost sodium were stopped 12 h before the study. Current smokers and patients with a history of smoking within the past 2 years were excluded from the study. This study was approved by the Human Subjects Research Committee of Shimane University Hospital. Written informed consent was obtained from all participants.

Measurements of forearm blood flow

Forearm blood flow (FBF, mL/min per 100 mL forearm tissue volume) was measured using mercury-filled silicone strain-gauge plethysmography as previously described elsewhere.[11,12] Briefly, a strain-gauge was placed in the widest part of the left forearm and the arm was slightly elevated above the level of the right atrium. The strain-gauge was connected to a Hokanson EC-5R Plethysmograph (Hokanson, WA, USA) that was calibrated to measure percent changes in volume, and this was connected in turn to a chart recorder to record the flow measurements. For each measurement, a cuff placed around the upper arm was inflated to 40 mmHg with a rapid cuff inflator (E-10, Hokanson, WA, USA) to occlude venous outflow from the extremity. A wrist cuff was inflated to suprasystolic pressure 1 min before each measurement to exclude the hand circulation. Flow measurements were recorded for 5 s every 15 s and four readings were obtained for each mean value.

Reactive hyperemia and blood sampling

All participants were instructed to abstain from eating food and drinking caffeinated beverages for at least 12 h before the study. The study was performed in the supine position in a room air-conditioned to a temperature of 25–26°C. After measurement of resting FBF, the effect of reactive hyperemia was measured. To induce reactive hyperemia, FBF was occluded by inflating the cuff on the left upper arm to 20–30 mmHg above the systolic blood pressure for 5 min. After the ischaemic cuff occlusion was released, FBF was measured for 5 min. The same procedure was repeated after an interval of 15 min. Forearm blood flow values were obtained by averaging the two measurements. Three parameters were used to assess the intensity of reactive hyperemia: maximum FBF; minimum forearm vascular resistance (FVR) calculated from mean blood pressure and FBF; and duration of reactive hyperemia defined as the interval (seconds) between the release of occlusion and the return to +5% of resting FBF.[11] Blood and urine samples were taken before the study. Serum analysis was performed for chemical factors including total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, glucose, haemoglobin A1c, vitamins C (ascorbic acid) and E, fibrinogen, thrombomodulin (TM), von Willebrand factor (VWF), highly sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6). The urinary concentration of 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) was also measured. Blood pressure was measured with a cuff sphygmomanometer placed on the contralateral arm at rest and every 1 min after release of cuff occlusion. These measurements were repeated at 4 and 8 weeks after enrolment in this study in the same manner.

Calculation of forearm blood flow

Forearm blood flow was calculated by two independent observers with no knowledge of the subjects' profiles, including the drugs used. Intra-observer and interobserver coefficients of variation were 2.1 ± 2.6% and 4.2 ± 3.6%, respectively, in resting FBF, 5.7 ± 4.9% and 7.2 ± 5.6% in maximum FBF, 6.5 ± 4.9% and 8.6 ± 5.9% in minimum FVR and 1.3 ± 3.1% and 2.6 ± 3.6% in duration of reactive hyperemia. In the preliminary study, the mean values in age- and gender-matched apparently healthy subjects (30 male and 18 female) were 2.95 ± 1.02 mL/min per dL in resting FBF, 31.15 ± 9.07 mL/min per dL in maximum FBF, 3.1 ± 1.1 mmHg/mL per min per dL in minimum FVR and 131 ± 27 s in duration of reactive hyperemia.

Laboratory measurements

Fasting blood samples were obtained at baseline and at the end of each 4-week period. Serum and EDTA plasma samples were stored at −80°C and analysed at the end of the study. Total cholesterol and LDL cholesterol were measured by enzymatic procedures. High density lipoprotein cholesterol was quantified after precipitation with phosphotungstic acid magnesium chloride. Frozen serum or plasma was used to measure ascorbic acid by high performance liquid chromatography, TM and VWF by enzyme immunoassay, hs-CRP by latex immunonephelometry and IL-6 by chemiluminescence enzyme immunoassay. Urine for measurement of 8-iso-$PGF_{2\alpha}$ was sampled in tubes containing indomethacin and stored at −80°C until the end of the study. Measurement of 8-iso-$PGF_{2\alpha}$ was performed by enzyme immunoassay (Assay Designs, MI, USA). The mean values in age- and gender-matched apparently healthy subjects (n = 30) in our laboratory were 7.5 ± 2.4 mg/dL in vitamin C, 1.5 ± 0.2 mg/dL in vitamin E, 280 ± 100 mg/dL in fibrinogen, 3.2 ± 1.5 FU/mL in TM, 128 ± 66% in VWF, 10 ± 6 × 100 ng/mL in hs-CRP, 1.5 ± 0.5 pg/mL in IL-6 and 142 ± 72 pg/mL in 8-iso-$PGF_{2\alpha}$.

Statistical analysis

At the follow-up for 8 weeks, four patients had dropped out because of infection (1 patient), brain attack (1 patient) and lumbago (1 patient) in the control group and diarrhea (1 patient) in the beraprost group. Statistical analysis was consequently performed for 11 patients in the control group and 14 patients in the beraprost group. Data are expressed as mean±SD unless otherwise indicated. A value of $P < 0.05$ was considered statistically significant. Intergroup differences were analysed with the chi-square test or unpaired t-test for baseline characteristics, except for BNP, hs-CRP, IL-6, VWF and 8-iso-$PGF_{2\alpha}$ levels. Either the Mann–Whitney U-test or Kruskall-Wallis analysis of variance (ANOVA) followed by Scheffe's post hoc test was used to compare the non-parametric variables BNP, hs-CRP, IL-6, VWF and 8-iso-$PGF_{2\alpha}$. Comparisons of time-course curves of percent changes in FBF during reactive hyperemia were analysed by two-way (group and study point) ANOVA for repeated measures followed by the Bonferroni correction for multiple-paired comparisons. Maximum FBF, minimum FVR and duration of reactive hyperemia were compared with two-way (group and study point) ANOVA followed by the Scheffe's post hoc test.

RESULTS

Baseline characteristics

The baseline clinical characteristics of the beraprost and control groups are shown in Table 1. There were no significant differences between the two groups in age, body mass index, blood pressure, heart rate, lipid data or haemoglobin A_{1c}. Coronary angiographic findings and left ventricular function were comparable, as were the drugs being administered, listed in Tables 2 and 3.

Table 1 The baseline characteristics of the study patients

	Control	Beraprost
n	11	14
Age (years)	72 ± 8	69 ± 6
Sex (M/F)	8/3	10/4
BMI (kg/m²)	23 ± 3	24 ± 3
Mean BP (mmHg)	83 ± 13	86 ± 9
HR (beats/min)	65 ± 13	59 ± 11
T-cho (mg/dL)	173 ± 31	170 ± 27
LDL-cho (mg/dL)	99 ± 27	104 ± 20
HDL-cho (mg/dL)	39 ± 9	42 ± 12
HbA1c (%)	5.8 ± 0.9	5.4 ± 0.5

Data are mean±SD. BMI, body mass index; BP, blood pressure; HR, heart rate; T-cho, total cholesterol; LDL-cho, low-density lipoprotein cholesterol; HDL-cho, high-density lipoprotein cholesterol.

Haemodynamics before and after administration of beraprost sodium

Haemodynamics during reactive hyperemia are shown in Table 4. At baseline, blood pressure and heart rate at rest were similar between the beraprost and control groups. Forearm blood flow at rest tended to be higher in the beraprost group than in the control group (3.60 ± 1.31 and 2.98 ± 0.46 mL/min per dL, respectively), but the difference was not statistically significant. During reactive hyperemia, mean blood pressure slightly but significantly decreased immediately after the occlusive cuff was released in both the beraprost group and the control group (86 ± 9 to 84 ± 7 mmHg and 83 ± 13 to 81 ± 10 mmHg, respectively; both $P < 0.05$). Heart rate tended to increase after release of the occlusive cuff, but the difference was not significant (data not shown). Maximum FBF were 22.97 ± 6.63 mL/min per dL in the beraprost group and 22.45 ± 3.03 mL/min per dL in the control group and there was no difference between the two groups.

Oral administration of beraprost sodium did not change blood pressure and heart rate, but significantly increased resting FBF to 4.18 ± 1.43 mL/min per dL ($P = 0.03$) and maximum FBF to 28.27 ± 8.89 mL/min per dL, $P = 0.01$) and returned to baseline 4 weeks after stopping beraprost sodium (22.58 ± 9.09 mL/min per dL). There were no changes in the haemodynamics of the control group. Percent changes in FBF from resting level during reactive hyperemia in the 105-s period after release of the cuff occlusion were significantly greater after 4 weeks of beraprost sodium treatment than at baseline in the beraprost group (Fig. 1). The duration of reactive hyperemia was unchanged over the 8-week course of the study in the control group. In the beraprost group, however, the duration of reactive hyperemia increased significantly from 77 ± 27 to 105 ± 46 s after 4 weeks of treatment with beraprost sodium ($P = 0.003$) and remained longer at 4 weeks after the beraprost sodium treatment was stopped (86 ± 28 s, $P = 0.02$) (Fig. 2).

Chemical factors before and after administration of beraprost sodium

Table 5 shows changes in chemical factors over the 8-week period for the two groups. At baseline, there were no significant differences in chemical factors between the beraprost group and the control group. In the control group, chemical factors remained unchanged through the follow-up, but in the beraprost group, beraprost sodium treatment significantly reduced urinary 8-iso-$PGF_{2\alpha}$ from 270 ± 221 pg/mL at baseline to 140 ± 53 pg/mL after 4 weeks of treatment ($P = 0.03$) and the value 4 weeks after beraprost sodium treatment was stopped tended to be lower than baseline (189 ± 116 pg/mL, $P = 0.07$). von Willebrand factor, hs-CRP and IL-6 did not change

Table 2 Clinical characteristics in study patients

	Control	Beraprost
Prior myocardial infarction (*n*)	8	9
Prior bypass graft surgery (*n*)	0	1
Prior angioplasty (*n*)	7	7
LVEF (%)	53 ± 9	59 ± 10
BNP (pg/mL)	95.6 ± 134.8	70.2 ± 112.4
NYHA (*n*)		
I	4	6
II	4	7
III	2	1
Coronary angiography (*n*)		
1-Vessel disease	4	11
2-Vessel disease	4	3
3-Vessel disease	2	0

Data are mean±SD. BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association Classification.

Table 3 Background therapies in study patients

	Control (%)	Beraprost (%)
ACE-I	7 (64)	9 (64)
ARB	4 (36)	4 (29)
β-blocker	6 (55)	8 (57)
Ca antagonist	9 (82)	11 (78)
Diuretics	2 (18)	2 (14)
Digitalis	1 (9)	1 (7)
Nitrate	10 (91)	12 (85)
Aspirin	11 (100)	13 (92)
Statin	3 (27)	4 (28)

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 4 Changes in haemodynamics at rest and during reactive hyperemia

	Rest					Reactive hyperemia		
	HR (b.p.m.)	SBP (mmHg)	DBP (mmHg)	FBF (mL/min per dL)	FVR (mmHg/mL per min per dL)	Max. FBF (mL/min per dL)	Min. FVR (mmHg/mL per min per dL)	Duration (s)
Baseline								
Beraprost	61 ± 11	125 ± 22	71 ± 11	3.60 ± 1.31	28.5 ± 10.9	22.97 ± 6.63	4.3 ± 1.4	77 ± 27
Control	68 ± 13	125 ± 19	69 ± 10	2.98 ± 0.46	28.9 ± 7.5	22.45 ± 3.03	4.8 ± 3.9	75 ± 11
4 weeks								
Beraprost	66 ± 10	125 ± 23	75 ± 14	4.18 ± 1.43*†	26.9 ± 17.6	28.27 ± 8.89*†	3.7 ± 1.0	105 ± 46*†
Control	66 ± 13	125 ± 18	73 ± 14	2.97 ± 0.65	28.9 ± 8.1	23.97 ± 4.45	4.6 ± 0.7	75 ± 21
8 weeks								
Beraprost	59 ± 10	125 ± 21	71 ± 11	3.99 ± 1.21	28.7 ± 6.8	22.58 ± 9.09	4.9 ± 2.5	86 ± 28*†
Control	59 ± 14	123 ± 16	70 ± 13	2.89 ± 0.83	29.8 ± 7.9	25.48 ± 5.10	4.2 ± 0.5	76 ± 12

8 weeks in the beraprost group indicates 4 weeks after stopping beraprost sodium. Data are mean±SD. DBP, diastolic blood pressure; FBF, forearm blood flow; FVR, forearm vascular resistance; HR, heart rate; SBP, systolic blood pressure.

*$P < 0.05$ versus corresponding value at baseline. †$P < 0.05$ versus corresponding control value.

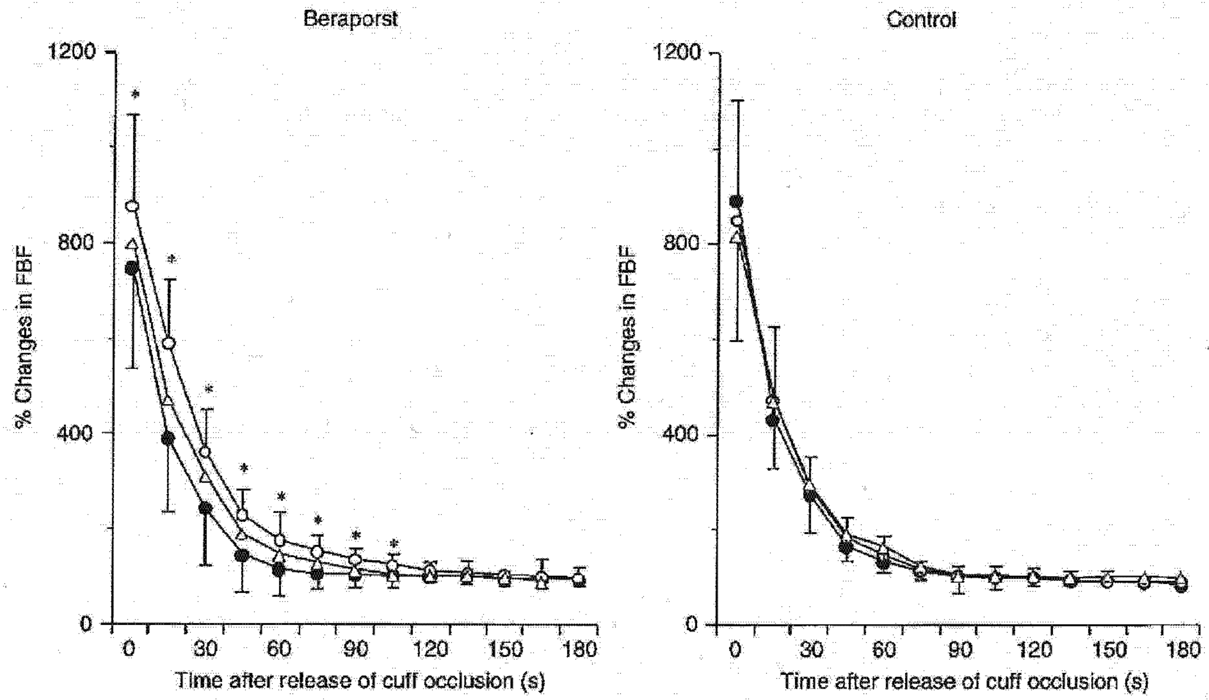

Fig. 1 Left panel: Percent changes in forearm blood flow from rest at baseline, after 4 weeks of treatment with beraprost sodium (4 weeks) and 4 weeks after treatment with beraprost sodium was stopped (8 weeks). Right panel: Percent changes in forearm blood flow from rest at baseline, after 4 weeks and 8 weeks without beraprost sodium treatment.

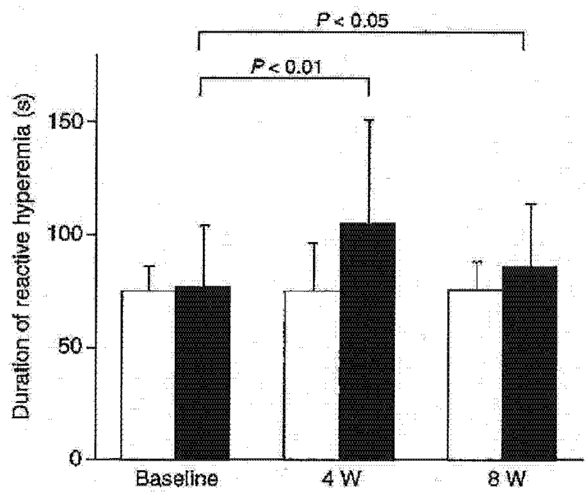

Fig. 2 Duration of reactive hyperemia at baseline, 4 weeks (4W) and 8 weeks (8W) in the control and beraprost groups. Data are expressed as mean±SD.

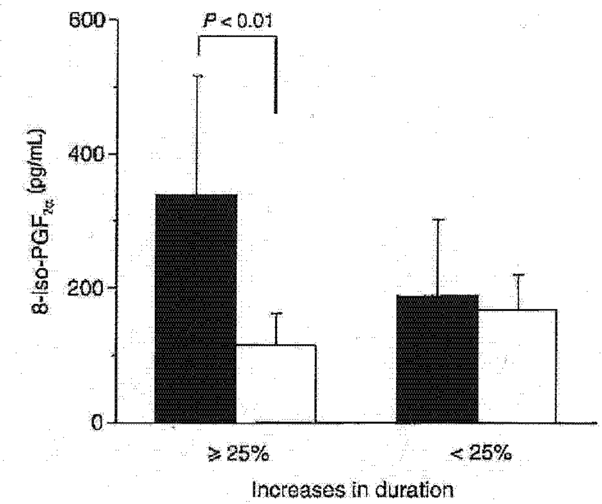

Fig. 3 Urinary concentration of 8-iso-$PGF_{2\alpha}$ at baseline and 4 weeks (4W) in patients in the beraprost group. Patients were classified into two patient groups based on the percent of increase, ≥ 25% and < 25%, in the duration of reactive hyperemia from baseline after 4 weeks treatment with beraprost sodium. Data are expressed as mean±SD.

significantly after 4 weeks of treatment in the beraprost group, but decreased significantly 4 weeks after treatment was stopped.

Relationship between duration of reactive hyperemia and 8-iso-$PGF_{2\alpha}$

The percent changes in duration of reactive hyperemia weakly but significantly correlated with the percent changes in 8-iso-$PGF_{2\alpha}$ ($r = 0.34$, $P < 0.001$). 8-iso-$PGF_{2\alpha}$ significantly decreased from 340 ± 275 to 117 ± 46 pg/mL ($P = 0.02$) after 4 weeks in those patients showing an increase in duration of reactive hyperemia ≥ 25% of baseline after beraprost sodium treatment, while it did not change in those patients without an increase in duration of hyperemia (from 190 ± 112 to 168 ± 52 pg/mL, $P = 0.69$; Fig. 3).

Table 5 Changes in venous and urinary concentrations of chemical factors

	Control			Beraprost		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Vitamin C (mg/dL)	7.2 ± 4.6	6.3 ± 2.6	6.8 ± 1.5	6.4 ± 2.7	6.4 ± 3.6	5.0 ± 1.5
Vitamin E (mg/dL)	1.00 ± 0.25	1.12 ± 0.38	0.86 ± 0.31	1.13 ± 0.25	1.12 ± 0.31	0.97 ± 0.28
Fibrinogen (mg/dL)	338 ± 101	282 ± 57	269 ± 66	298 ± 115	272 ± 45	200 ± 23
TM (FU/mL)	3.3 ± 1.2	3.4 ± 1.1	3.2 ± 1.5	3.5 ± 1.6	3.5 ± 1.5	3.9 ± 1.9
VWF (%)	198 ± 89	182 ± 69	179 ± 66	180 ± 48	151 ± 41	125 ± 39*†
hs-CRP (× 100 ng/mL)	30 ± 33	25 ± 33	28 ± 38	29 ± 31	19 ± 17	13 ± 15*†
IL-6 (pg/mL)	3.1 ± 1.9	3.7 ± 2.7	3.4 ± 1.6	2.6 ± 1.5	2.8 ± 0.8	1.8 ± 0.7*†
8-iso-$PGF_{2\alpha}$ (pg/mL)	238 ± 183	220 ± 257	218 ± 86	270 ± 221	140 ± 53*†	189 ± 116*

8 weeks in the beraprost group indicates 4 weeks after stopping beraprost sodium. Data are mean±SD. hs-CRP, highly sensitive C-reactive protein; IL-6, interleukin 6, 8-iso-$PGF_{2\alpha}$; 8-iso-prostaglandin $F_{2\alpha}$; TM, thrombomodulin; VWF, von Willebrand factor.
*$P < 0.01$ versus corresponding value at baseline. †$P < 0.05$ versus corresponding control value.

DISCUSSION

The salient finding of this study is that oral administration of beraprost sodium, a long-acting and orally active stable analogue of PGI_2, resulted in an increase in reactive hyperemia as an index of endothelium-dependent vasodilatation in patients with coronary artery disease. In addition, urinary 8-iso-$PGF_{2\alpha}$, a marker of oxidative stress was reduced significantly by treatment with beraprost sodium. These findings suggest that the beneficial effects of beraprost sodium on the vascular endothelium in patients with coronary artery disease is associated with a reduction in oxidant stress. Furthermore, the forearm vasoreactivity enhanced by treatment with beraprost sodium was still observed even 4 weeks after the treatment was stopped.

Effects of beraprost sodium on vascular endothelial function

Numerous previous studies have demonstrated the beneficial effects of acute and chronic therapeutic interventions such as lipid-lowering,[14–16] angiotensin-converting enzyme inhibition,[17,18] physical activity, L-arginine,[19] and anti-oxidant therapy[20] on endothelial function in the forearm and have shown that some of these resulted in lowering the cardiovascular event rate. However, there have been only a few reports on the effect of beraprost sodium on the endothelium. Since Sakai *et al.*[10] first demonstrated the cytoprotective effect of beraprost sodium against chemical injury in cultured human vascular endothelial cells, experimental studies have reported the beneficial effects of this agent on impaired endothelial cells. Matsumoto *et al.*[9] showed that impairment of the vasodilator response of the abdominal aorta to acetylcholine was restored by treatment with beraprost sodium for 28 days in the diabetic rat. In a clinical setting, Nishimura *et al.*[21] measured TM and plasma tissue-type plasminogen activator before and after treatment of patients with diabetes by oral administration of beraprost sodium for 1 month and demonstrated its favourable effect on endothelial function. Recently, Tomiyama *et al.*[22] demonstrated that single administration of beraprost sodium increased reactive hyperemia in the forearm associated with a decrease in plasma TM level in patients with coronary artery disease, suggesting acute effects of beraprost sodium on vascular endothelial function. In the present study, despite beraprost sodium not being administered on the study day, vasoreactivity in the forearm was significantly increased by treatment for 4 weeks. These previous and present results indicate a beneficial effect of beraprost sodium on impaired endothelial function. The favourable effects might lead to a decrease in cardiovascular events, though the efficacy of treatment with beraprost sodium for symptoms in patients with peripheral arterial disease has been conflicting among previous reports.[7,8] Long-term studies should be performed in the future to confirm the beneficial effects of beraprost sodium on the endothelial function and the prevention of cardiovascular events.

Mechanisms of beneficial effects of beraprost sodium on the endothelium

It is well known that PGI_2 is an unstable eicosanoid secreted by the vascular endothelial cells that produces strong vasodilatation[2,23] and suppresses platelet aggregation,[1,24,25] thus supporting blood circulation. Beraprost sodium has been developed as a long-acting and orally active stable analogue to PGI_2[26] that mimics the biological properties of PGI_2, such as activation of adenylate cyclase and elevation of intracellular cAMP levels, through activation of the PGI2 receptor.[27,28] Elevated cAMP activates protein kinase A, which inhibits cytokines, the transmembrane receptor tissue factor, E-selectin and vascular cell adhesion molecule-1 in human monocytic and endothelial cells, leading to a cytoprotective effect on the endothelium.[29,30] Previous studies have furthermore demonstrated many favourable effects on endothelial cells, such as an anti-inflammatory effect,[31] inhibition of superoxide,[32–34] and up-regulation of hepatocyte growth factor[9] and TM expression from the endothelial cells.[28]

In the present study, beraprost sodium augmented the reactivity of the forearm vessels in patients with coronary artery disease and the degree of augmentation of hyperemia correlated with the reduction of urinary 8-iso-$PGF_{2\alpha}$, suggesting that this drug has an antioxidative effect in patients with high oxidative stress, leading to improvement of impaired endothelial function. This possibility is supported by previous experimental studies demonstrating inhibition of superoxide production from human[33] and rat[34] neutrophils. As another mechanism, the increased resting FBF after treatment with beraprost sodium might also contribute to the enhanced reactivity of the forearm vessels, since endothelial cell function might be enhanced by elevated shear stress in a flow-dependent manner. However, it is difficult to ascertain a precise mechanism for this phenomenon from our results. It is interesting that although IL-6 and hs-CRP were not affected by beraprost sodium after 4 weeks, they were significantly lower than at baseline 4 weeks after the treatment was stopped. This was accompanied by a decrease in VWF after 8 weeks, suggesting a reduction in endothelial cell damage. The duration of reactive hyperemia was also still greater than at baseline 4 weeks after the treatment was stopped. These findings might suggest that beraprost sodium increases the vasoreactivity via the antioxidative effects in the early stage of treatment and that the effects might link to suppression of inflammation and cytokine production, leading to an increase in vasoreactivity even after treatment is stopped. However, our results do not allow us to draw any conclusions as to whether the beneficial effects of beraprost sodium arise from a direct or indirect effect on the endothelial cells. Furthermore, it is difficult to explain the prolonged anti-inflammatory effects after the cessation of treatment. Niwano *et al.*[35] recently reported that beraprost sodium increased the steady-state levels of endothelial nitric oxide synthase (eNOS) mRNA and protein in cultured human aortic endothelial cells, indicating NO-mediated protective effects on the vascular endothelium, whereas PGI_2 had little effect on eNOS gene expression. Their study might suggest the possibility that beraprost sodium directly evoke eNOS gene expression in the endothelial cells, leading to prolonged anti-inflammatory effects via increased NO production. However, PGI_2 receptor has not been identified on the endothelial cells. To clarify this issue, additional studies will be needed in future.

Study limitations

The present study has several limitations. First, there is methodological limitations in measurement of blood flow by plethysmography. Although blood flow values obtained by plethysmography correlate with actual flow, they may under- or over-estimate the actual flow in some patients.[36] However, this limitation may be obviated by the fact that the present study focused on changes in blood flow in individual patients rather than absolute blood flow values. Second, is the effect of background therapies on endothelial function. In the present study, treatment with angiotensin converting enzyme inhibitor, angiotensin receptor blocker and statins, which have been reported to improve endothelial dysfunction,[17,37–39] were continued throughout the study. Although these agents were unchanged throughout the study, we cannot exclude the possibility that these drugs influenced the present results. Third, is a difference in severity of coronary artery disease between the two groups. The control group included two patients with 3-vessel disease, whereas the beraprost group did not. However, we did not find any effect on reactive hyperemia even in four patients with 1-vessel disease in the control group. Finally, the small number of subjects and the lack of placebo control limit the statistical power of the data and may perhaps mask differences between the two groups.

CONCLUSIONS

The present study demonstrated that beraprost sodium, a stable analogue of PGI_2, caused an augmentation of reactive hyperemia in the forearm of patients with coronary artery disease accompanied by a reduction in urinary 8-iso-$PGF_{2\alpha}$ levels. These findings indicate a cytoprotective effect on vascular endothelial cells for beraprost sodium. These phenomena might contribute to the protective effects of beraprost sodium on cardiovascular events, which have been suggested in previous studies.[7,8] Further studies are needed in a larger sample size and in a placebo control study to confirm our findings.

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●症 例●

Cisplatin 肝動注療法と TS-1 経口投与が奏効した膵腺房細胞癌肝転移の1例

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板倉 正幸 板垣 友子 西 健 遠藤真一郎 樋上 哲哉*

〔*Jpn J Cancer Chemother* 33(4): 525-528, *April*, 2006〕

Pancreatic Acinar Cell Carcinoma Successfully Treated with Combination of Oral TS-1 and Intra-Arterial Cisplatin:
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Summary

Pancreatic acinar cell carcinomas are rare, and little is reported on their chemotherapy. We report a 49-year-old male patient with pancreatic acinar cell carcinoma and multiple liver metastases, which responded to oral TS-1 and hepatic arterial infusion of cisplatin. The patient underwent a partial hepatectomy, MCT abrasions and excision of the pancreatic tumor. Postoperative pathological studies revealed metastases of acinar cell carcinoma to the liver and lymph nodes; the primary lesion was undetermined. After surgery, the patient was treated with hepatic arterial infusion of cisplatin and oral TS-1. Metastatic tumors completely disappeared, and serum lipase decreased to normal levels. Abdominal CT one year after surgery revealed a pancreatic body tumor, which was surgically removed. Pathological studies showed primary pancreatic acinar cell carcinoma, while previous metastases remained under control. To summarize, TS-1 and cisplatin can be effective treatments for pancreatic acinar cell carcinomas. Key words: Acinar cell carcinoma, TS-1, Hepatic arterial infusion (*Received Sep. 5, 2005/ Accepted Nov. 9, 2005*)

要旨 膵腺房細胞癌はまれで，その化学療法に関する報告は少ない。今回，TS-1経口投与とcisplatin肝動注療法が奏効した膵腺房細胞癌肝転移の1例を経験した。症例は49歳，男性。糖尿病の経過中に膵体部腫瘤と多発性肝腫瘍を発見された。術前にTS-1を経口投与後，膵体部腫瘍摘出および肝外側区域切除とMCT焼灼術を行った。病理診断は腺房細胞癌で，膵体部腫瘍は転移リンパ節と診断され，原発巣の所在は不明であった。術後TS-1経口投与およびcisplatin肝動注を行い，肝転移は消失した。しかし約1年後の腹部CTで膵体部腫瘤を認め，再手術を行った。肝転移はコントロールされており膵腫瘍を摘出した。病理診断は原発性膵腺房細胞癌であった。一般に予後不良とされる膵腺房細胞癌に対してTS-1とcisplatinの併用療法が有効である可能性が示唆された。

はじめに

膵腺房細胞癌（acinar cell carcinoma: ACC）はまれで，その化学療法に関する報告は極めて少ない。今回，TS-1経口投与とcisplatin（CDDP）肝動注療法が奏効したACCの1例を経験したので報告する。

I．症 例

患者: 49歳，男性。

主訴: 全身倦怠感。

既往歴: 20年前，十二指腸潰瘍穿孔で幽門側胃切除術。5年前よりアルコール依存症，糖尿病。

家族歴: 兄が膵癌で死亡。

現病歴: 2002年9月，上記主訴で近医受診。CA19-9の上昇と腹部超音波検査で3cm大の膵体部腫瘤と4〜5cm大の多発性肝腫瘤を認め当科紹介となった。

入院時現症: 身長155cm，体重47kg。貧血（−），黄疸（−）。右季肋部に腫大した肝を触知し，圧痛を認めた。

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片岡 佳樹
0385-0684/06/¥500/論文/JCLS

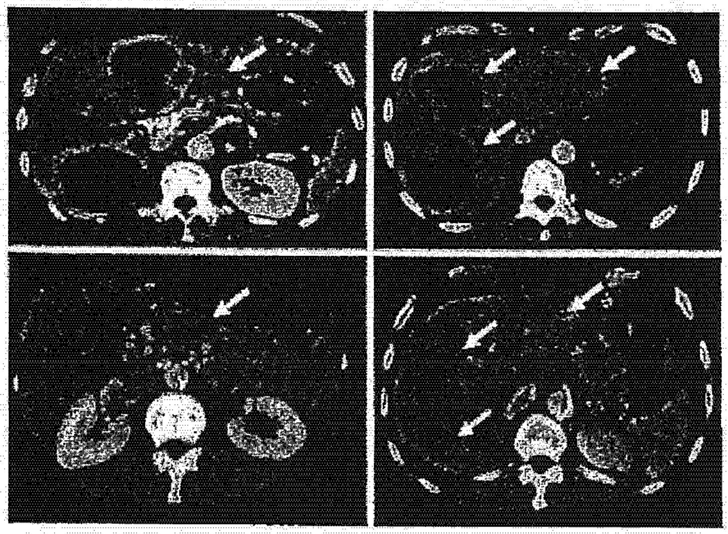

図 1
入院時造影 CT
a: 膵体部上縁に 45×30 mm 大の境界明瞭，内部不均一な腫瘤を認める（矢印）。
b: 肝両葉に辺縁が造影される多数の腫瘤を認める（矢印）。
1 年後造影 CT
c: 膵体部に新たな腫瘤を認める（矢印）。
d: 肝転移巣は縮小している（矢印）。

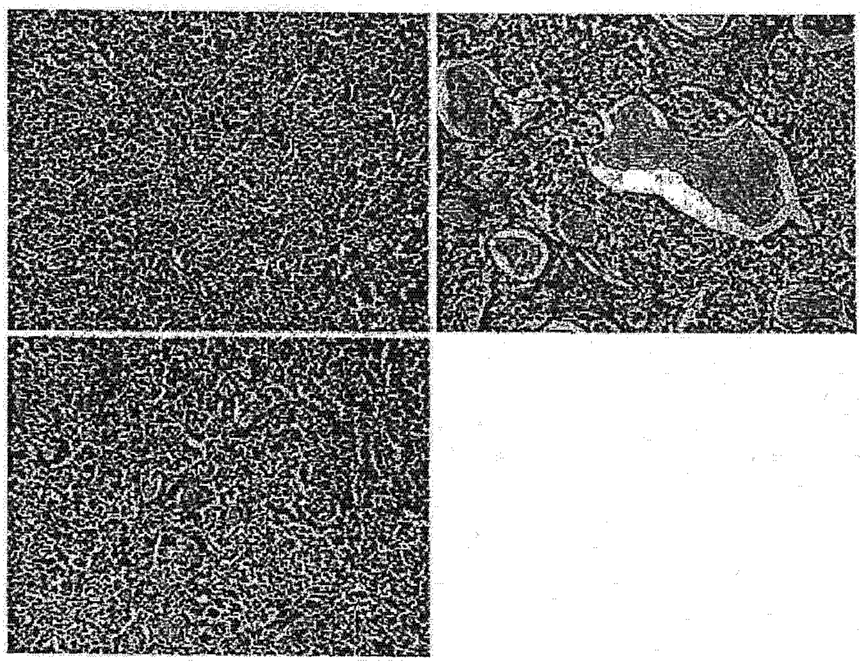

図 2　病理組織所見（HE 染色 200 倍）
a: 肝腫瘍，b: 転移リンパ節，ともに比較的均一な腫瘍細胞が腺房様構造や充実状構造を示していた。
c: 膵体部腫瘍は前回の転移巣同様，腫瘍細胞が腺房様構造を示していた。

臍上部にも弾性硬の腫瘤を触知した。

入院時血液生化学検査: リパーゼ 8,620 IU/l，CA19-9 130 U/ml，DUPAN-II 471 U/ml，SPan-1 73.4 U/ml と上昇していた。

入院時造影 CT: 膵体部上縁に 4.5 cm 大の境界明瞭，内部不均一な腫瘤を認め（図 1 a），肝両葉に辺縁が造影される腫瘤を多数認めた（図 1 b）。

初回手術所見: 膵癌の多発性肝転移の診断で，術前に

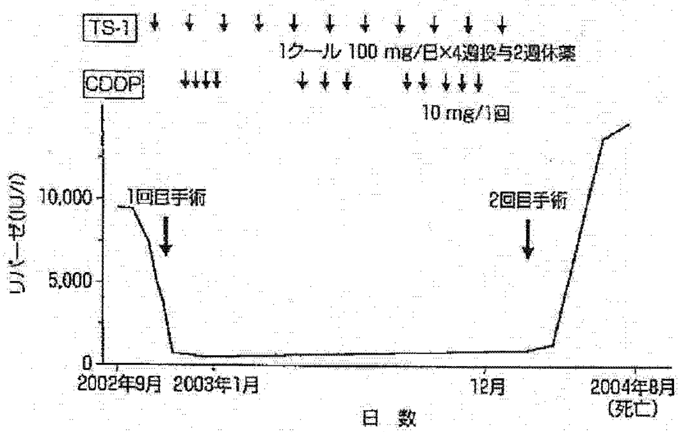

図 3　治療経過

表 1　膵腺房細胞癌に対する化学療法の本邦報告例

No.	年齢/性	腫瘍部位 径（cm）	転移	手術	薬剤	投与法	放射線	効果	転帰	発表者 年
1	69/男性	膵頭部 (6.5)	腹膜播種	腫瘍摘出	5-FU, Ara-C MMC, ADR, OK-432	全身		PR	3 か月 死亡	Ono 1984[3]
2	23/女性	膵頭部 (不明)	肺 肝（術後 4 年） 再肺（術後 6 年）	PD	5-FU, CDDP OK-432	全身 肝動注		PR	99 か月 死亡	神谷 1993[4]
3	41/女性	膵頭体部 (4.8)	なし	胃空腸吻合	EPIR, MMC 5-FU	肝動注		PR	7 か月 死亡	藤木 1996[5]
4	56/男性	膵体尾部 (9.5)	肝（術後 8 か月）	膵体尾部 横行結腸切除	5-FU, CDDP MMC	肝動注		CR	17 か月 生存	左近 1996[2]
5	47/男性	膵尾部 (不明)	肝	膵尾部切除	5-FU, ADR MMC	肝動注		不明	9 か月 死亡	森井 1998[6]
6	53/男性	膵頭部 (9)	肝	なし	ADR, MMC 5-FU	肝動注	40 Gy	CR	33 か月 生存	和田崎 2000[7]
7	68/女性	膵鈎部 (2.3)	肝	PD 肝部分切除	RF＋化学療法	不明		不明	不明	松田 2001[8]
8	50/男性	膵体尾部 (10)	肺，頸部，縦隔 腹部リンパ節	なし	CDDP, 5-FU	全身		PR	13 か月 死亡	明石 2001[9]
9	63/女性	膵頭部 (5)	肝	なし	5-FU CBDCA	肝動注		PR	8 か月 死亡	山内 2001[10]
10	33/男性	膵頭体部 (8)	門脈浸潤	なし	CDDP, 5-FU	肝動注		PR	7 か月 生存	森 2004[11]
11	49/男性	膵体部 (3)	肝	腫瘍摘出 肝部分切除 MCT 焼灼術	CDDP, TS-1	肝動注		PR	21 か月 死亡	自験例 2005

TS-1 内服を 1 クール行い，2002 年 11 月初回手術を行った。肝外側区域および S 6，S 7，S 8 に腫瘍を認め，肝外側区域切除術と，S 6，S 7，S 8 の腫瘍に対し MCT を施行，膵体部前面の腫瘍は摘出した。

摘出標本（初回手術）: 外側区域の肝腫瘍は 7.0 cm 大，膵体部腫瘍は 4.5 cm 大で，割面はいずれも白色充実性であった。

病理組織所見（初回手術）: 肝腫瘍，膵体部腫瘍はともに比較的均一な腫瘍細胞が腺房様構造や充実状構造を示していた（図 2 a，b）。免疫染色では cytokeratin 7（CK 7）陽性で，膵 ACC と診断されたが，膵体部腫瘍は転移リンパ節と診断された。

全治療経過: 術後は外来で TS-1 の内服（1 クール 100 mg/日×4 週投与 2 週休薬）と CDDP 10 mg/回（原則として 1 回/週）の肝動注を行い，リパーゼ値は急激に減少し正常化した（図 3）。この間副作用としては軽度の骨髄抑制がみられただけであった。

1 年後造影 CT: 術後 1 年目の造影 CT で肝転移巣は縮

小したが新たに膵体部に3 cm大の腫瘤を認め，これが原発巣と考えられた（図1c，d）。

2回目手術所見: 2004年2月，膵体部腫瘍を摘出した。腫瘍は主膵管壁に浸潤していたため，これを一部合併切除し胃後壁と側々吻合した。

摘出標本(2回目手術): 膵体部腫瘍は2.0 cm大で，割面は白色充実性であった。

病理組織所見（2回目手術）: 組織学的には前回とほぼ同様で，免疫染色でも α_1 antitrypsin，CK 7がともに陽性で原発性膵ACCと診断された（図2c）。

2回目術後経過: 術後4か月目の造影CTでは腫瘍の再発はみられなかったが，アルコール依存症のため18か月目から治療を自己中止し，21か月目に再発死亡された。

II. 考　察

膵ACCの頻度は膵外分泌腫瘍の約0.79%と比較的まれである[1]。その臨床的特徴として，発見時すでに遠隔転移を認める進行例が多いとされる。治療では化学療法が重要な役割を果たすと考えられるが，確立された化学療法はない[2]。膵ACCに対する化学療法の本邦報告は，集計した限りでは自験例を含め11例であった（表1）[2-11]。男性7例，女性4例で，年齢は23～69歳(平均50.2歳)であった。9例（81.8%）に遠隔転移を認め，7例が肝転移であった。切除は6例（54.5%）に行われていた。化学療法の効果は不明2例を除いた9例中CR 2例，PR 7例で，生存期間は3～99か月であった。CRの2例は，化学療法として5-FU，MMCとCDDPまたはADRの組み合わせで，PRの7例でも5-FU系の薬剤が使用され5-FUを中心とした化学療法が有効であると考えられた。一方，肝転移がみられた7例中6例に肝動注が行われ，CR 2例，PR 4例と全症例有効であった。自験例は，減量的肝切除とMCTを行った後CDDP肝動注療法を行い，肝転移を制御し得た。初回術後1年目に明らかとなった原発巣に対し腫瘍摘出を行った。その理由は肝転移が良好にコントロールされていたためで，他臓器転移を有する場合には低侵襲でかつ減量効果が得られる腫瘍摘出術も術式の一つのoptionと考えられた。

結　語

一般に予後不良とされる膵ACCに対し，TS-1とCDDPによる併用療法が有効である可能性が示唆された。

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特集　外科外来の小手術～プライマリーケアのために～

下肢静脈瘤

菊地　慶太*　樋上　哲哉*2

はじめに

下肢静脈瘤は日常臨床のなかでよく目にする疾患である。下肢静脈瘤を診察するにあたり，どのように検査を行い，病状にあった治療法を選択するかが大切である。

I. 下肢静脈の解剖（図1a）

下肢の静脈は，①下肢静脈の本管である深部静脈，②大伏在静脈や小伏在静脈などの表在静脈，③表在静脈から深部静脈へ血液を送る交通枝，穿通枝と，大きく3つに分けられる。下肢静脈瘤の原因となるのは表在静脈である大・小伏在静脈やその分枝である。大伏在静脈は卵円窩を介して深部静脈に還流するが，その場所では（図1b）のように5本の分枝がみられる。手術における再発予防には，これらの分枝を確実に処理することが重要[1]となる。

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key words：下肢静脈瘤，ストリッピング術，硬化療法

II. 病　　因

下肢静脈瘤とは，下肢静脈のうっ血により静脈や交通枝における弁の機能不全，もしくは穿通枝の機能不全を生じて表在静脈が拡張，蛇行したものである。その病因から一次性静脈瘤と二次性静脈瘤に分けられる。

1. 一次性静脈瘤

深部静脈には異常がなく，立ち仕事，出産などにより静脈がうっ血して生じたものであり，女性に多い。いわゆる手術の適応となる静脈瘤はこの一次性静脈瘤である。

2. 二次性静脈瘤

深部静脈の閉塞により二次的に発生した弁不全による静脈瘤である。慢性静脈不全の状態にあり，色素沈着や硬結，潰瘍を合併することが多い。

III. 症　　状

一次性静脈瘤では，静脈の怒張や蛇行などが気になり，美容に関した愁訴により来院することが多い。また症状としては，長時間の立位による下肢倦怠感や腫脹による疼痛を訴える。「夕方になると足が張る・重い・痛い」と訴えることが多い。血栓性静脈炎を併発すると硬結

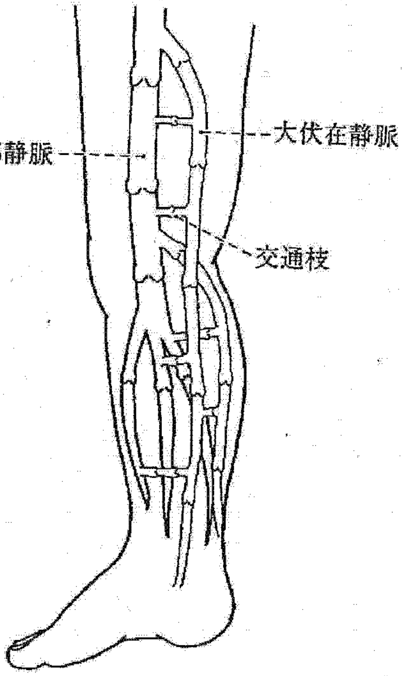

図 1a　下肢静脈

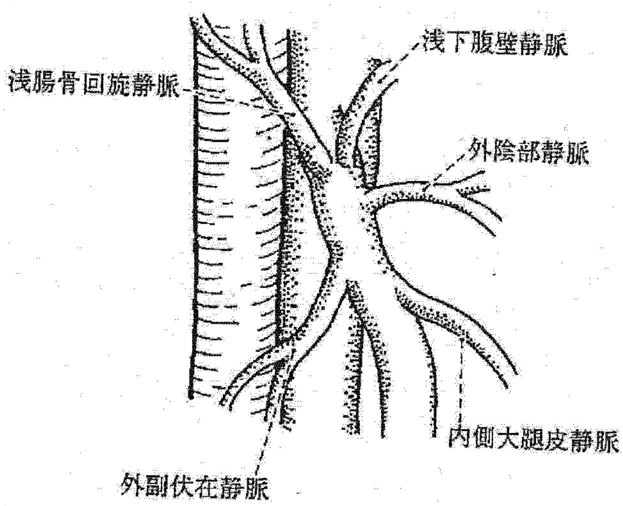

図 1b　卵円窩の解剖


図 2a　大伏在静脈瘤

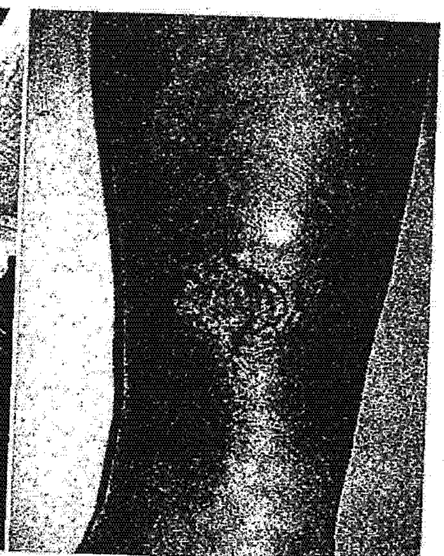
図 2b　潰瘍を伴う一次性静脈瘤

や発赤，疼痛を伴う。

二次性静脈瘤では，強い浮腫からの倦怠感や疼痛を訴えることがある。また，皮膚の硬化や色素沈着，病状が悪化すると下肢潰瘍を呈することがある。

形態からは，①伏在静脈瘤，②側枝静脈瘤，③網目状静脈瘤，④クモの巣状静脈瘤に分類される[2)3)]。図 2a は一次性静脈瘤の大伏在静脈瘤である。夕方の下肢痛を主訴としストリッピング術を行った。図 2b は慢性うっ血による難治性潰瘍を併発した症例である。この症例は深部静脈血栓症を認めなかった。

IV. 診断のための検査

検査で大切なことは，深部静脈が開存しているか否かの診断と，弁不全や交通枝不全の診断である。

1. Brodie−Trendelenburg 検査（図3）

ベッド上で仰臥位とし，患側肢を挙上し静脈瘤を空虚としたあと，大腿上部を駆血帯で緊縛するか深部静脈への流入部（卵円窩）を圧迫したままで立位とする方法である。起立後に静脈瘤が空虚のままであれば，末梢の交通枝の弁不全はない。立位で静脈瘤が出現する場合は，交通枝の弁不全がある。また，圧迫を解除すると静脈瘤が直ちに出現する場合には，圧迫部や大伏在静脈中枢部の弁不全があると診断できる。

2. Perthes 検査

起立した状態で駆血帯により大腿上部を緊縛する。その後屈伸運動を行い静脈瘤が空虚になれば，交通枝の弁には問題ない。静脈瘤が消失しないか，かえって増大する場合は深部静脈血栓症が存在する。

3. 下肢の周径計測（図4a）

下肢大腿部と下腿の最大周径を計測し，左右差や経時的変化から浮腫の程度を評価する。

4. Doppler 血流計（図4b）

外来でも低侵襲で簡単にできる。静脈の血流

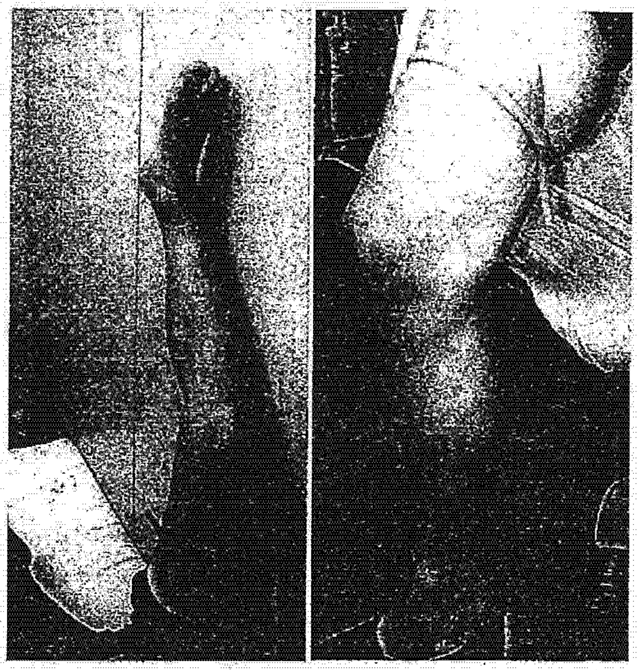

図3　Brodie−Trendelenburg 検査
立位になっても静脈瘤は空虚のままである。交通枝の弁不全がないことがわかる。

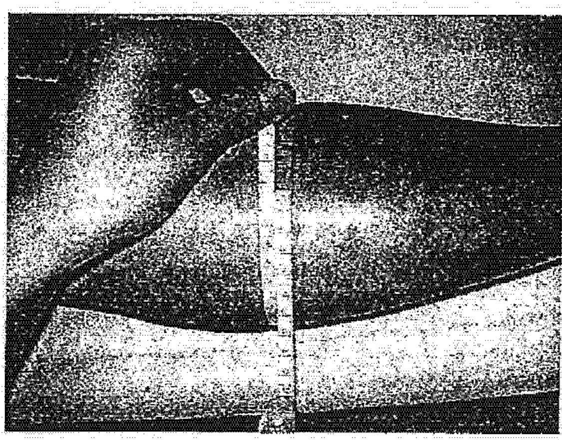

図4a　下肢周径計測は下腿の最大径の部位を計測し，周径の変化により浮腫の程度を確認する。

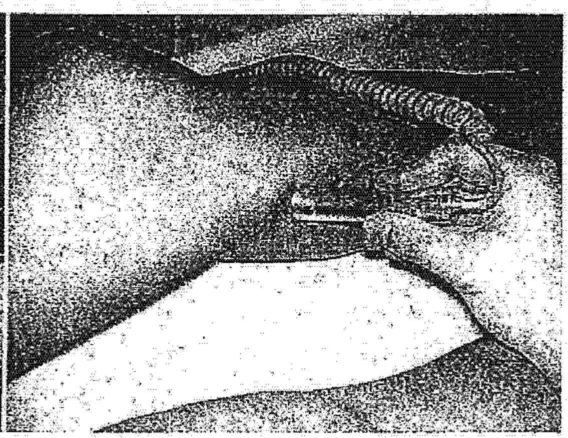

図4b　Doppler 血流計により，弁不全による逆流や交通枝不全を検出する。

音を聴取し，逆流の有無から弁不全を確認できる。また，不全交通枝や動・静脈瘻の部位を術前に特定し，手術で結紮する。

5. 超音波検査

深部静脈の血流評価（血栓の有無），弁不全の有無（逆流評価）を低侵襲で評価する。

6. 静脈造影検査

足背皮静脈から造影剤を注入して深部静脈の開存の有無，不全交通枝の診断を行う。

V. 治療法とそのタイミング

治療の適応であるが，美容上の主訴で来院することが多く，症状がなくても静脈瘤が存在すれば治療の対象となる。現在行われている下肢静脈瘤の治療は，①弾性ストッキングの着用，②高位結紮術や硬化療法，③ストリッピング術などが挙げられる。2003年に行った静脈疾患サーベイ委員会の調べ[4]では，ストリッピング術が全体の37%を占めもっとも多く，ついで硬化療法や結紮術の組み合わせが30%であり，これらの治療法が主体である。大伏在静脈本管の静脈瘤に対しては，ストリッピング術が主であり，小伏在静脈瘤や分枝静脈瘤，また形態的には，網目状静脈瘤やクモの巣状静脈瘤などが硬化療法や結紮術の適応となる。

1. 弾性ストッキングの着用

浮腫の強い症例はもちろん，浮腫がなくても静脈瘤があればストッキング着用を勧める。

2. 硬化療法と結紮療法

硬化療法[5]は，静脈瘤内に硬化剤を注入することで血管内皮細胞を傷害して，血管内腔を癒着し閉塞させることを目的とした治療法である。硬化剤として0.5～3%のポリドカノール（1～2%ポリドカノールが多い）を用いたり，14.6%の高張食塩液であるコンクライトNaを用いる。患者をベッド上に仰臥位とし，硬化療法を行う静脈瘤を穿刺する（中枢側を駆血すると行いやすい）。硬化剤を注入するときには，下肢を挙上して静脈瘤内の血液を除去する。この操作が血管の癒着を確実なものとする。注入時は注入部位を押さえて静脈血の流入を防ぎ，ゆっくり注入する。注入後は注入した部位の圧迫を弾性包帯やストッキングの着用まで継続する。

結紮療法では，大伏在静脈自体の結紮・切離はもとより，卵円窩にある大伏在静脈の5分枝を確実に結紮・切離することが大切である。膝上・下部において可能なかぎり長く大伏在静脈を切除したり，硬化療法の併用が再発予防に寄与すると報告される[1]。小伏在静脈においても同様の手技を行う。

VI. 手　術

臥位になると静脈瘤の場所がわかりにくくなるために，手術直前に切除を行う予定の静脈瘤と交通枝，鼠径切開予定部位などをマジックでマーキングしておく（図5a）。医療ミスを予防する意味からもきわめて重要である。

ストリッピング術は，まず鼠径部で大伏在静脈が深部静脈に流入する卵円窩を露出する。鼠径靭帯における大腿動脈の拍動部位から末梢に二横指内側に二横指の部位（図5b）を斜切開する。この部位にある大伏在静脈の五分枝（図1b）を結紮・切離する。次に末梢部位で大伏在静脈を露出し，結紮したのちにストリッパー（図6a）を静脈内に挿入していく。中枢側から挿入する場合には，分枝に入らないように，また弁で引っ掛かるために，手で弁を変形して進めていく。末梢側から挿入する場合には，交通枝を介して深部静脈に進まないように注意する。いずれの場合にも，ストリッパー先端を手で確認しながら進めていく（図6b）。また，静脈瘤は蛇行することが多く，途中でストリッパーが止まったならば，その部位で大伏在静脈を露出して静脈抜去を行う。

静脈抜去は伏在神経損傷に対する配慮から，

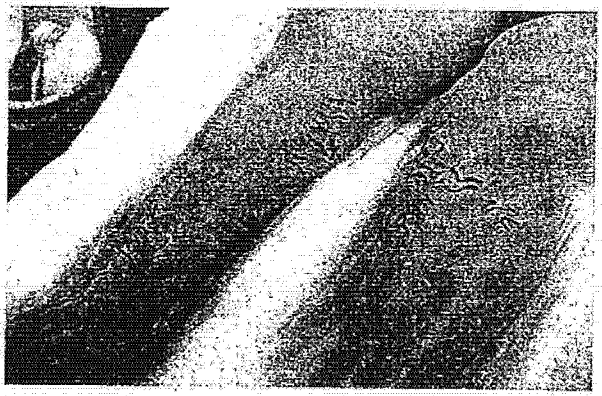

図 5a　術前マーキングでは，手術予定部位の静脈瘤や伏在静脈にマジックで印をつけておく。また，不全交通枝などの位置も×印をつけておくとよい。

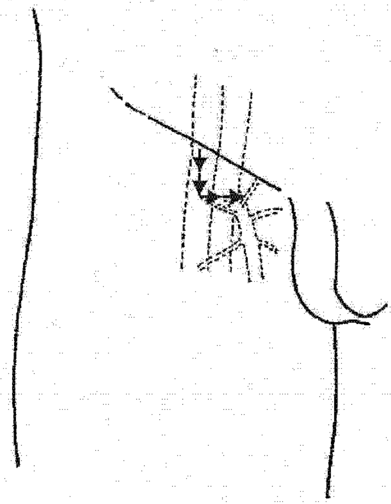

図 5b　鼠径切開部は，鼠径靱帯下縁の大腿動脈拍動部位から大腿動脈に沿って2横指末梢，その2横指内側に卵円窩があるので，同部位を皮膚割線に沿って約3～5 cm 切開する。

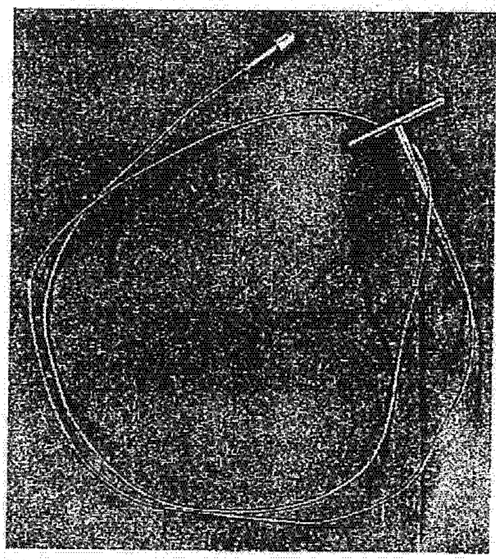

図 6a　ストリッパー

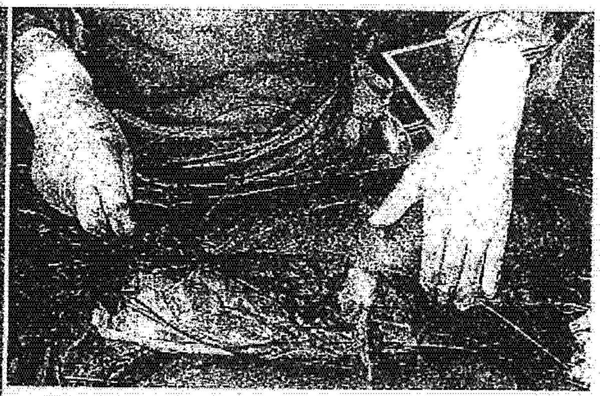

図 6b　ストリッパーの挿入時には，片手で先端を確認しながら静脈に沿ってゆっくり挿入する。

中枢から末梢側への抜去が望ましいとされる[6][7]。静脈抜去後は約5分間の圧迫止血を行う。蛇行の強い部位では，あらかじめ大伏在静脈を露出しておくとよい。静脈の抜去に伴い，分枝の静脈瘤も末梢側まで剝離し切除する。剝離はMetzenbaumの刃先を若干開けて，静脈周囲の脂肪組織をそぎ落とすように行うとよい。途中で筋膜内に入っていく交通枝を確認したら，結紮・離断しておく。この操作を根気よく繰り返していく。静脈瘤抜去後の閉創は皮下

をしっかり結節縫合し，皮膚は埋没縫合を行うことで，術後早期に退院するにあたり，消毒や抜糸の必要がなく管理が容易である。最近では0.1% リドカインにエピネフリン，重炭酸ナトリウムを添加したTLA（tumescent local anesthesia）液を大量に使用する局所麻酔法であるTLA法により，ストリッピング術を日帰りで行う手術[8]も報告されている。

おわりに

静脈瘤の手術は，研修医として臨床現場に出てから，初めて行う手術となる場合が多く，確実な外科基本手技が要求される。また，手術だけではなく硬化療法や高位結紮術などを組み合わせて，再発や合併症のない確実な治療を行っていくことが大切である。

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