Immersing feet in carbon dioxide-enriched water prevents ulcer expansion and ulcer formation after surgical revascularization in critical limb ischemia: a preliminary trial

（重症虚血肢の下肢動脈外科的血行再建術後における
潰瘍増悪・新規形成予防に対する人工炭酸泉足浴の効果）

名古屋大学大学院医学系研究科
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平成20年度学位申請論文

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（指導：山田純生 教授）

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CONTENTS

Introduction

The current clinical consensus is that critical limb ischemia (CLI) with multi-level-disease requires adjunctive treatments after surgical revascularization.[1] Adjunctive treatments should prevent postoperative problems such as amputation, ulcer exacerbation and graft occlusion. Although recent studies have focused on the effects of medication,[2,3] a number of alternatives including spinal cord stimulation,[4] hyperbaric therapy,[5] and an intra-muscular injection of autologous bone-marrow mononuclear cells,[6] which may be also beneficial in revascularized CLI. However, the efficacy as adjunctive treatments for revascularized CLI remains unclear.

In 1997, Hartmann et al.[7] reported that immersion in water enriched with carbon dioxide had positive microcirculatory effects. In 2002, we demonstrated that CO_2 immersion increased the blood flow of feet to the much higher extent than the plain water, and it improved the limb salvage rate in CLI patients without revascularization option.[8] Using experimental animals, Irie et al.[9] recently showed that CO_2 immersion induced local VEGF production, resulting in NO-dependent neocapillary formation associated with mobilization of endothelial progenitor cells. These results suggest that CO_2 immersion could be an effective adjunctive treatment to prevent early postoperative amputation and ulcer exacerbation.

Based on these previous findings, the present study evaluated the hypothesis that immersion of feet in CO_2-enriched water can prevent expansion or formation of ischemic ulcer after surgical revascularization of CLI in patients with advanced type Ⅱ diabetes.

Materials and Methods

Patients and setting. Study was conducted at Nagoya Kyoritsu Hospital between November 2004 and November 2007 for diabetic patients after lower limb revascularization. Two experienced surgeons diagnosed and performed the surgical revascularization. The patients were eligible for participation if they had CLI clinically defined by extremity pain at rest requiring use of analgesics for at least 2 week or the presence of ischemic ulcer before surgical revascularization, and had type C or D lesions[10] in the infrainguinal artery that were detected by preoperative angiography. In addition they had hemodynamic failure in the below knee artery that were detected by postoperative ultrasonography. Patients were excluded from the study if they had ulcers that expose bone, tendon or fascia, because the immersion of these feet in water may increase the risk of severe infection. Patients were ineligible if they had clinically infected ulcers, severe heart failure (New York Heart Association Class Ⅲor Ⅳ), malnutrition (serum albumin <2.5 g/dL), or a history of autoimmune disease affecting the vascular system. Patients were excluded if they enrolled in a clinical evaluation of another wound-care device or drug.

All patients provided written informed consent in order to participate in this study, which was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the School of Health Sciences, Nagoya University, Nagoya, Japan (approval number 5-512), and was approved by the Ethics Committee of Nagoya Kyoritsu Hospital, Nagoya, Japan.

The patients were randomly assigned to receive either topical treatment (CO_2

immersion plus standard care; CO_2 group) or standard care alone (control group) using the concealed envelope method.

Standard care. Both groups received medication of Ticlopidine (300-600 mg/day), Cilostazol (200 mg/day), or Sarpogrelate (200-300 mg/day) in addition to Aspirin (81-162 mg/day). Patients with ischemic ulcers received wound cleansing, debridement (as required at the discretion of the vascular surgeons) and dressing changes. All patients were required to wear treatment shoes that provide depressurization for ischemic ulcers.

Carbon dioxide-enriched water bath (CO_2 immersion). The CO_2 group immersed their feet in CO_2 enriched water (depth of 20-30 cm, 37-38°C, duration for 10 minutes) every day, during hospitalization. After discharge, they received CO_2 immersion at least 3 times per week for the next 3 months at our outpatient clinic. The CO_2 enriched water is made with an extra corporeal circulation system (MRE-SPA-MD, Mitsubishi Rayon Engineering, Tokyo, Japan) .[8,9] It can instantly enrich 5 L/min of tap water (pH 6.8) with CO_2 (free CO_2 concentration, 1,000 to 1,200 mg/l, pH 4.6). Patients recorded the immersion dates, which were confirmed by the investigators.

Patient follow-up. The primary endpoint was defined as the expansion of a target ulcer to 101% or more of the original size and/or formation of a new ulcer during the follow-up period. Patients were censored from the analysis at the time of their last study contact if they were lost to follow up before the assessment at 3 months after surgery (for discontinued therapy due to hospitalization, withdrew consent, or social problems). All time-dependent occurrences of endpoints were quantified within the study period in both groups. The patients were also evaluated with respect to hemodynamic parameters (see below) at the end of follow-up period and the values were compared with those obtained at immediately after surgery. All measurements were performed by four expert physical therapists.

Ulcer evaluation. Ischemic ulcers were photographed from the same direction every two weeks. Dimensions were determined from the longest edge-to-edge measurement (length) of the ulcer and the longest ulcer dimension perpendicular to the length (width).[11] Ulcer size was defined as: length × width of ulcer (cm).

Hemodynamic measurements. Transcutaneous oxygen pressure ($tcPO_2$) and transcutaneous carbon dioxide pressure ($tcPCO_2$) were measured using an oxymonitor (PO850, Sumitomo Electric System Solutions, Tokyo, Japan). Skin blood-flow (SBF) was measured using a laser Doppler flow-meter (ALF-21, Advance, Tokyo, Japan). Measurement sites were located on the dorsal surface of the affected feet of patients seated (probe 80-85 cm below heart level) in a standardized environment with an ambient temperature of 25 ± 2°C, relative humidity 60%, and air movement at < 0.1 m/s. After swabbing the skin with alcohol, the $tcPO_2$ probe was positioned 3.0 cm proximally to the first interdigital fold as the skin was heated to 43.5ºC. The laser Doppler probe was positioned 2.5 cm proximally to the fourth interdigital fold.[12] When a stable steady-state was achieved (20 min after fixing the probes), data were continuously acquired for 5 min using an automated recorder (Power Lab, Bio Research Center, Tokyo, Japan), and the mean value during the final minute was adopted.

All patients rested for 10 min in the supine position, and then ankle pressure (AP), ankle brachial pressure index (ABI), toe pressure (TP), and toe brachial pressure index (TBI) were measured using an ABI-form (BP-203RPEII, Colin, Tokyo, Japan). The ABI and TBI were calculated as the ratio of ankle systolic pressure divided by brachial systolic pressure and as the ratio of hallucis systolic pressure divided by brachial systolic pressure, respectively.

Statistical analysis. Demographic and baseline variables were compared using Chi-square test and Mann-Whitney test. Prevention of ischemic ulcer expansion was estimated using the Kaplan-Meier method. The cumulative values of preventing expansion or formation of ischemic ulcer were analyzed using a log rank test. The analysis was conducted based on the principle of the intention-to-treat.[13] Changes in variables from baseline to after 3 months and differences between the groups were analyzed using Wilcoxon signed rank test and Mann-Whitney test based on per-protocol. *P*-values <.05 were considered to indicate statistical significance. All data were analyzed using Statistical Package for the Social Sciences, version 15.0 (SPSS Inc. Chicago, Illinois).

Results

Patients. Initially, from 78 limbs of 66 patients screened for inclusion, 70 limbs of 59 patients were finally enrolled in this study. These patients were allocated CO_2 group (34 limbs of 28 patients) and control group (36 limbs of 31 patients) (Figure 1).

The CO_2 group and control group did not differ with respect to baseline characteristics (Table 1).

The distribution of conduit type, bypass procedure and values for immediately postoperative hemodynamic measurements were similar for both groups (Table 2). There were many cases who did not have a suitable autogenous vein for distal bypass graft. Namely, 16 out of 28 patients in CO_2 group (57%) and 18 out of 31 patients in control group (58%) have undergone the coronary bypass operation using great saphenous veins. Five patients in each group underwent infragenicular revascularization with autogenous vein. Before surgery, the enrolled 31 limbs (44%) showed AP<50mHg, and another 39limbs(56%) showed either TP or $tcPO_2$ in consistent with the CLI criteria. [1]

Effects of CO_2-immersion on ischemic ulcer expansion after surgical revascularization. Figure 2 shows Kaplan-Meier plots demonstrating the effect of CO_2 immersion on ischemic ulcer expansion or formation after surgical revascularization. In the control group, the rate of prevention of ischemic ulcer (y-axis) began to decrease after day 20 and reached 77.8% after 90 days. In contrast, in the CO_2 group, the rate of prevention remained at 100% until 60 days and then slightly decreased to 97.1% at 90 days. In other words, ischemic ulcers were exacerbated in 1 limb in the CO_2 group, while, in control group, new ulcer developed in 2 limbs and pre-existing ulcers became exacerbated in 6 limbs. The difference in the cumulative values of the prevention of ischemic ulcer expansion after 3 months in the CO_2 group and control group was statistically significant (P = .012). In exacerbated limbs, expansion of a target ulcer >150% of the original size were commonly observed. Among them, major amputation was performed in two limbs in the control group, but in none in the CO_2 group. Deep wound infection was observed 4 limbs in the control group only. The ulcer size (length x width, in cm) was significantly reduced in the CO_2 group (2.9 ± 2.5 to 1.6 ± 1.9 in 13 limbs over 3 months; P < .001), but not in the control group (2.4 ±1.6 into 2.4 ± 1.4 in 8 limbs, over 3 months; P =.06).

Among enrolled, 11 patients (6 in CO_2 group and 5 in control group) were discontinued due to several reasons: 2 died (one in each group), 1 for exacerbation of CHF (in CO_2 group), 2 due to the second surgery for graft failure (one in each group), and 6 were censored by consent withdrawn or social problems (three in each group).

Effect of CO_2 immersion on the tissue oxygen pressure. The mean $tcPO_2$ value increased in 3 months in the CO_2 group, while that in the control group did not increase during this period. Accordingly, after 3 months, $tcPO_2$ became significantly higher in the CO_2 group than in the control group. However the mean $tcPCO_2$ and SBF did not change in both groups (Table 3). Other parameters, AP, ABI, TP, TBI, also did not change significantly.

Discussion

In the present study, we report that the expansion and formation of ischemic ulcers was successfully prevented for 3 months by immersing feet in CO_2-enriched water after surgical revascularization for CLI in diabetic patients. Consistently, the $tcPO_2$ values were remarkably improved in the CO_2 group, but remained unchanged in the control group. These results strongly suggest that CO_2-immersion is effective against ulcer exacerbation, presumably due to the elevation of $tcPO_2$.

Previously, the rates of limb salvage as well as that of graft patency were followed for relatively long periods after surgical revascularization of CLI patients.[14-17] These reports suggested that despite patent grafts of infrainguinal bypass, patients with end-stage renal diseases often developed extensive necrosis of extremities that resulted to amputation. In the early postoperative stage, ulcer exacerbation could often be overlooked; however, it leads to major complications. Therefore, early postoperative ulcer expansion and new ulcer formation should be evaluated as well as the graft patency. Ulcer healing after revascularization may be affected by many factors including nutrition (represented by serum albumin level), preoperative ulceration, and lesion severity.[18] Amann et al.[19] identified the importance of microcirculatory perfusion as the ultimate cause of ischemic tissue loss. Ubbink et al.[20] suggested that ischemic ulcers of non-reconstructable CLI might heal without major intervention if local microcirculation is well preserved.

Herein, we showed that average of $tcPO_2$ in the CO_2 group increased more than 10% after 3 months, whereas that of the control group remained unchanged. Hartmann et al.[7] demonstrated that immersion in CO_2-enriched water increases $tcPO_2$ by 10% and immediately increases laser Doppler output three-fold in patients with mild peripheral occlusive arterial disease. In this context, we previously showed that immersion in CO_2-enriched water causes vasodilation, even in patients with non-reconstructable CLI and improved the limb salvage of CLI patients.[8] This work led us to examine the efficacy of CO_2 immersing as an adjunctive treatment following surgical revascularization. The increased supply of oxygen may be an underlining mechanism for the prevention against ulcer expansion and new ulcer formation. Using experimental animals, it has been shown that CO_2 immersion results in a NO-dependent increase in collateral blood perfusion, induction of regional VEGF synthesis, and mobilization of endothelial-lineage progenitor cells into the circulation.[9] These results suggest that CO_2 immersion improves subcutaneous microcirculation.

The $tcPO_2$ value has been used as an index to quantify local microcirculation in ischemic regions to determine the amputation level and predict therapeutic effects.[21-23] Furthermore, the $tcPO_2$ value has confirmed a substantial intra-class correlation coefficient and variability, and a smaller variance than that of the AP, TP, and ABI measured by trained observers.[24] In the CO_2 group, the $tcPO_2$ improved by >10% from baseline indicates clinically significant changes.[25] The $tcPO_2$ was elevated by CO_2 immersion, without affecting the blood pressure at either the ankle or toe. These results suggest that the physiological mechanism for prevention of ulcer exacerbation by CO_2 immersion is the improvement of subcutaneous microcirculation.

Serious complications, such as major amputation of limb and/or deep wound infection with target ulcer, occurred only in the control group. It is tempting to speculate that CO_2 immersion prevents bacterial infection. The pH of CO_2-enriched water is acidic (pH 4.6) and stabilizes hypochlorous acid (HOCl); thus, it exhibits a strong bactericidal action, since stabilized HOCl has potential pharmaceutical applications in the control of soft tissue infection.[26] However, further investigation with a larger number of patients will be required to confirm this notion.

Finally, we must mention the study population. All of the enrolled patients suffer from type Ⅱ diabetes and approximately 70% of them are receiving hemodialysis due to chronic renal failure. Also, they have been suffering from coronary artherosclerosis and often received coronary bypass operation using autogenous veins. This caused the shortage of the available vein and this was one of the reasons why the large number of revascularization was limited above knee vessels and only 10 limbs out of 70 underwent infragenicular revascularization with autogenous vein (Table2). Though there were no significant difference in patients' characteristics between CO_2 group and control group, the ratio of smokers and duration of the hemodialysis tend to be slightly higher and longer in control group than CO_2 group. These factors might modify the results, so the further investigation will be needed to clarify this point. As CO_2 immersion increases local oxygen supply by improving subcutaneous microcirculation, such a regimen could be used as an adjunctive treatment for the prevention of ischemic ulcer expansion at limb with CLI, not only in diabetic patient but also in general CLI. To prove this, a long-term follow-up study is on the way with a larger number of patients suffering from various diseases, with or without CO_2 immersion.

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Table 1 Patients' characteristics

	CO_2 group	Control group	*P* value
Number of patients	28	31	
Age (years)	69±10	66±7	*0.31*
Male [n]	20（71％）	24（77%）	*0.77*
Insulin therapy [n]	16（57%）	17（55%）	*1.00*
Hemoglobin A1c (%)	6.7±0.9	6.5±1.1	*0.59*
Hypertension [n]	22 (79%)	23 (74%)	*0.77*
Hyperlipidemia [n]	9 (32%)	10 (32%)	*1.00*
Smoking [n]	6 (21%)	13 (42%)	*0.11*
History [n]			
CAD	23 (82%)	26 (84%)	*1.00*
CVD	7 (25%)	9 (29%)	*0.78*
COPD	4 (14%)	7 (23%)	*0.51*
Hemodialysis [n]	19 (68%)	22（71%）	*1.00*
Duration of hemodialysis (months)	72±53	104±69	*0.12*
Albumin（g/dL）	3.5±0.4	3.4±0.4	*0.32*
Medication [n]			*0.77*
Aspirin	28 (100%)	31 (100%)	
The other antiplatelets in addition to aspirin	19 (68%)	23 (74%)	

Note: Variables are mean ± standard deviation.
Abbreviations: CAD, coronary artery disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease.

Table 2 Distribution of bypass procedure, conduit and hemodynamic measurements of immediately after surgery

	CO_2 group	Control group	*P* value
Number of affected limbs	34	36	
Indication of revascularization			*1.00*
Rest pain	20 (59%)	22 (61%)	
Ulceration	14 (41%)	14 (39%)	
Bypass procedure [n]			*0.94*
Axillo-femoral bypass	4 (12%)	3 (8%)	
Femoral-femoral bypass	2 (6%)	4 (11%)	
Femoral-popliteal bypass (above knee)	23 (67%)	24 (67%)	
Femoral-popliteal bypass (below knee)	1 (3%)	1 (3%)	
Popliteal-below knee bypass	4 (12%)	4 (11%)	
Conduit type [n]			*1.00*
Prosthesis	29 (85%)	31 (86%)	
Autovein	5 (15%)	5 (14%)	
Hemodynamics immediately after surgery [n]			
AP < 50mmHg	8(24%)	12(33%)	*0.43*
TP <30mmHg	11(32%)	16(44%)	*0.34*
$tcPO_2$<50mmHg*	13(38%)	15(42%)	*0.81*

Note: Variables are mean ± standard deviation.
Abbreviations: AP, ankle pressure; TP, toe pressure; $tcPO_2$, transcutaneous oxygen pressure.
*, seated

Table 3 Mean scores and standard deviations for all outcome variables, immediately after surgery and 3 months later by group

	CO_2 group			Control group		
	Immediately after surgery	3 months	P value	Immediately after surgery	3 months	P value
$tcPO_2$ (mmHg)*	56±14	63±15†	＜0.01	54±15	57±13	0.81
$tcPCO_2$ (mmHg)*	38±10	37±6	0.06	39±8	39±7	0.96
SBF(ml/min/100g)*	1.8±1.4	1.4±0.9	0.46	1.6±1.0	1.4±0.7	0.21

Note: Variables are mean ± standard deviation.
Abbreviations: $tcPCO_2$, transcutaneous carbon dioxide pressure; SBF, skin blood flow.
*, seated
†, *P*<.01 vs. immediately after surgery (CO_2 group)

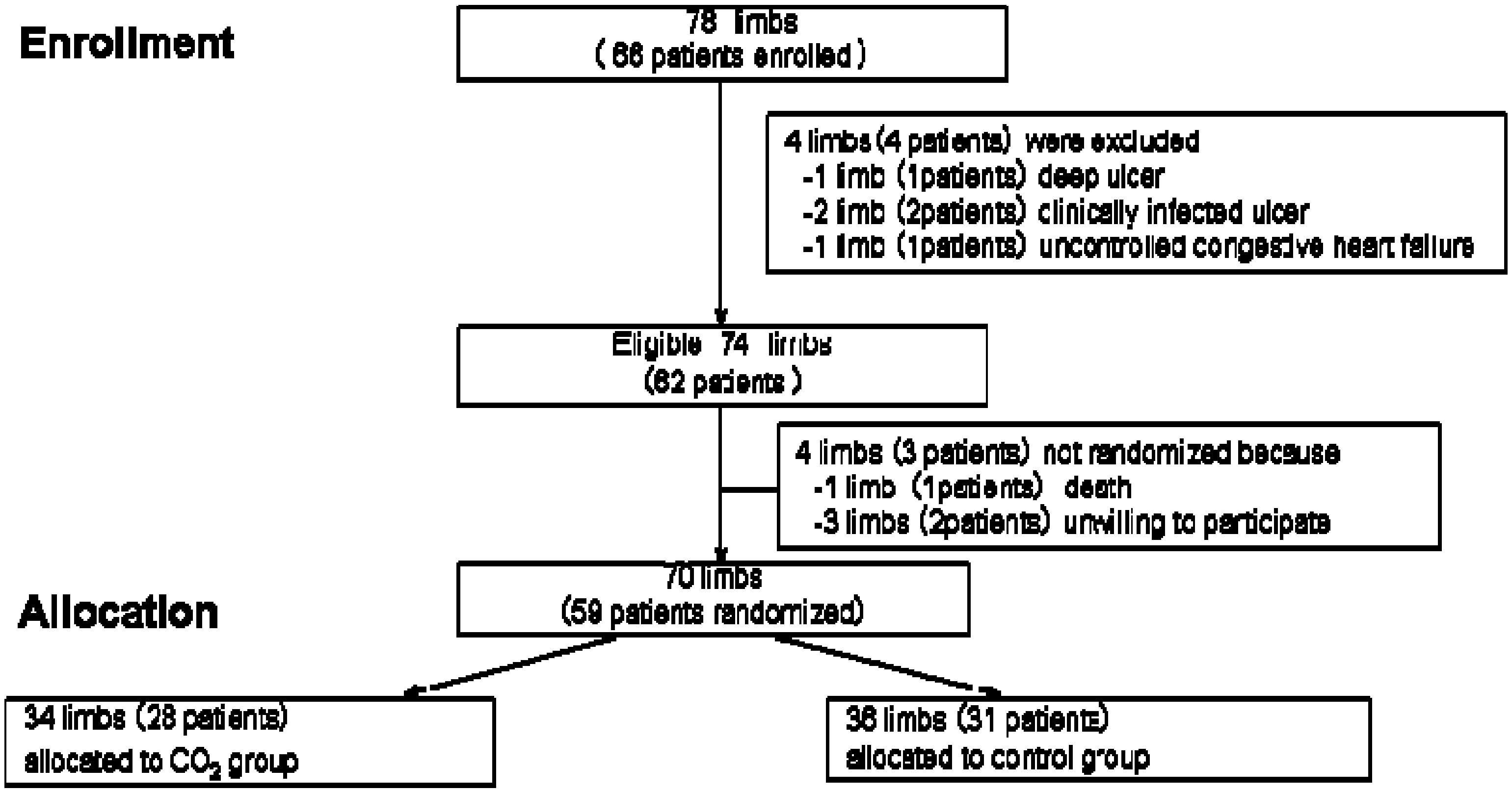
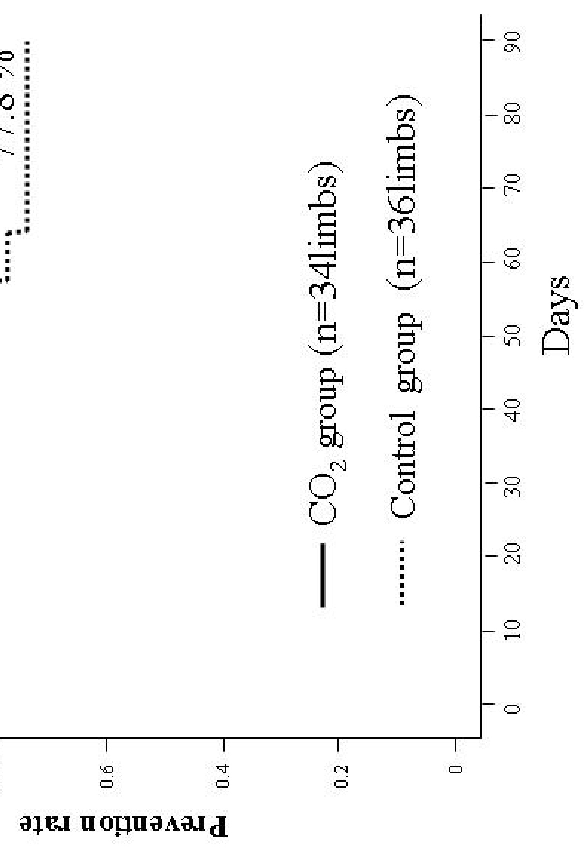

Enrollment
78 limbs
(66 patients enrolled)
4 limbs (4 patients) were excluded
-1 limb (1patients) deep ulcer
-2 limb (2patients) clinically infected ulcer
-1 limb (1patients) uncontrolled congestive heart failure
Eligible 74 limbs
(62 patients)
4 limbs (3 patients) not randomized because
-1 limb (1patients) death
-3 limbs (2patients) unwilling to participate
70 limbs
(59 patients randomized)
Allocation
34 limbs (28 patients)
allocated to CO2 group
36 limbs (31 patients)
allocated to control group

Fig 1.



Prevention rate
1.0
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
90
Days
97.1%
77.8 %
CO_2 group (n=34limbs)
Control group (n=36limbs)

Fig 2.

Figure Legends

Figure 1. Flow chart of the clinical trial.

Figure 2. Prevention rate for formation and expansion of ischemic ulcer in CO_2 group and control group.

A Kaplan-Meier plot was created with respect to the prevention rate (Y axis), i.e., the number of limbs free from ulcer aggravation / number of enrolled limbs in each group. “Free from ulcer aggravation” is defined as ulcer expansion of less than 101% of the original size and/or absence of newly formed ulcers. A significant difference was observed between CO_2 group and control group (P = .012 by log-rank test).

和　文　抄　録

Immersing feet in carbon dioxide-enriched water prevents ulcer expansion and ulcer formation after surgical revascularization in critical limb ischemia: a preliminary trial

（重症虚血肢の下肢動脈外科的血行再建術後における潰瘍増悪・新規形成予防に対する人工炭酸泉足浴の効果）

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【目的】潰瘍増悪ならびに新規形成予防率を成果指標とし、2 型糖尿病患者の重症虚血肢に対する外科的血行再建術後の補助療法として、人工炭酸泉足浴の効果を検討する。

【方法】対象は 2004 年 11 月から 2007 年 11 月の間に名古屋共立病院 ASO センターにて下肢動脈血行再建術が施行された 2 型糖尿病患者とした。適格基準を満たす症例を人工炭酸泉足浴実施群と基本治療群に割付け、術後 3 ヶ月間追跡を行った。人工炭酸泉足浴(温度 37～38℃、CO_2 濃度 1,000 - 1,200mg/ℓ、水深 20-30cm、10 分/回)は、週に 3 回以上実施した。割り付けられた群に関わらず、基本治療として薬物療法および潰瘍に対する処置・免荷を行った。観察期間中に新規潰瘍形成および潰瘍増悪（潰瘍径が 1%以上拡大した場合）が確認された症例は観察終了とし、両群の潰瘍増悪ならびに新規形成予防率を比較した。

【結果】適格基準を満たした 62 例 74 肢中、周術期死亡 1 例、研究参加拒否 2 例を除く 59 例 70 肢が人工炭酸泉足浴実施群（28 例 34 肢）および基本治療群（31 例 36 肢）に割り付けられた。両群の疾患背景および下肢血行動態に有意差は認められなかった。

3 ヶ月間の潰瘍増悪・新規形成予防率は人工炭酸泉足浴実施群 97.1%、基本治療群 77.8%と人工炭酸泉足浴実施群で有意に高いことが明らかとなった（$P=0.012$, log-rank test)。また、血行動態指標については足背部経皮的酸素分圧のみ、人工炭酸泉足浴実施群で有意な上昇が認められた（$P<0.01$, Wilcoxon signed rank test)。

【結論】人工炭酸泉足浴は基本治療と併用して行なうことで、潰瘍増悪および新規形成予防効果が得られ、2 型糖尿病患者の重症虚血肢に対する術後早期治療成績向上に寄与することが示唆された。