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Physiological Effects of Carbon Dioxide Treatment on Diabetic Foot Ulcer Patients

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Abstract
Background*: Diabetic foot ulcer (DFU) considers one of the most anxious complications associated with uncontrolled diabetes mellitus. The aim of this study is to evaluate carbon dioxide therapy on patients with DFU and compare with patients on traditional therapy.* ***Methods****: 100 patients with DFU (mean age 51.6+ 5.65 years; 56men) divided into two groups ,traditional therapy group will be treated using advance dressings and antibiotics, while CO2 therapy group will be treated using advance dressings and CO2 therapy. ABI and Doppler measured Blood flow to the affected foot; also, the size, color and sensation of the ulcerative area were all evaluated and compared between two groups.* ***Results****: Results showed improvement of blood flow to the affected foot as well as improvement in the sensation , size and color of the ulcerative area .****Conclusion****: effectiveness of this method in the treatment of ischemic feet, and indicates it is potential utility as a form of physiotherapy in the treatment of ischemic feet .*

Keywords– *DFU: Diabetic foot ulcer, ABI: Ankle Brachial Index, CO2: carbon dioxide.*

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I. Introduction :

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by high blood sugar levels that result from defects in insulin secretion, or action, or both. Diabetic foot ulcers (DFU) are one of the major concerns of the complication of DM. it was affect health-related quality of life in various dimensions, such as physically, mentally, socially, and economically[1,2] .Foot ulcers precede about 85%xof all diabetic lower-extremity amputations[3,4] . Carboxytherapy is the use of carbon dioxide (CO2)-rich water bathing which was firstly developed in France in 1930.It was found that CO2 helped in wound healing[5] .The effect ofxCO2 enriched water lies primarily in the vasodilatation which is due to the increase in nitrous oxide formation by CO2xleading to vasodilatation and release of growth factor for angiogenesis which increases oxygen delivery to the area [6] . The same principle is applied in the treatment of DFU that increase delivery of CO2 to the ulcerated area, which will generate nitrous oxide liberation that will mediate the sequence of events that end up with increase oxygen and blood flow to the ulcerated feet. The improved angiogenesis and oxygenation will result in healing of the ulceration[7] , Also it determines relaxation of the smooth muscle cells in the metarterioles and precapillary sphincters with a consequent increase in the flow velocity and improvement in the tissue perfusion. This enhanced vasomotion and increase in local tissue perfusion [8].

II. Patients And Methods

Data collection: The study was included 100 patients with diabetic foot (59 males and 41 females), with mean age of 51.8±5.8 years and range between 35-65 years old. The patients will selected by etiology and wound extension and randomly will divided into two groups (CO2 therapy group and Traditional therapy group). Traditional therapy group will be treated using dressings alone, while CO2 therapy group will be treated using dressings and CO2 therapy.

Inclusion criteria: The study population comprised male and female patients with diabetic food ulcer. Supplementing the drug regimen of subjects with new agents or introducing new treatments was avoided during the study period.

Exclusion criteria: The patient excluded from the study are those with severe heart failure, malnutrition, or a history of disease affecting the vascular system also, those how have renal dieses and liver dieses. Patients who have been enrolled in a clinical treatment of another wound-care device or drug.

Ethical statement: The patients provided written informed consent prior to enrollment into the study. Ethical committee at Medical college university of Baghdad appeared no obligations or interventions put to interfere with standard care of patients. The study.

Questionnaire: A special questionnaire was designed by the investigator and by supervisors to collect the information by interview.
The questionnaire included:
- Demographic data (age, residence, occupation).x
- Full history was taken from the patient including (Previous medical and surgical history, the duration of diabetic, and drug history).x
- Thorough physical examination was done including: Ulcer (wound) evaluation and sensory examination of the area (foot) [size of ulcer, colour, and depth of ulcer and position of ulcer].

Ulcer Evaluation: Foot ulcers were photographed from the same angle at beginning and at end of study. Dimensions were determined from the longest edge-to-edge measurement (length) of the ulcer and the longest ulcer dimension perpendicular to the length (width)[9] .Also by, examine this parameter: size of the ulcerative area, color and sensation of the foot.
Ulcer size was defined as length × width of ulcer (cm).The size, depth and position of the ulcer have to be recorded, which measured by metered ribbon.
The following scale evaluated the color: (1 = normal skin, 2 = pink with no necrotic areas, 3 = blue minor necrosis, 4 = yellow, medium necrosis and 5 = black, deep necrosis).
The sensation of the area was evaluated by pressure pin performed by a dermatologist and the scale was (1 = normal sensation, 2 = fair, 3 = slight sensation, 4 = poor sensation, and 5 = no sensation)[10]
Blood sample collection and processing: Five milliliter of venous blood was aspirated from each subject to be used for measurement of blood sugar and HbA1c, also Renal Function Test, Liver Function Test and lipid profile,these tests were done on patients first visit before we started the study to ensure both group are equal in their investigation and there general health . The blood sample was taken from the patients in fasting state.
Doppler ultrasound: This test uses ultrasound to assess the blood flow in the large arteries and veins in the legs. This test was done in the first visit and at the end of the study. Patients made to lie on USG couch in supine position for evaluation of iliac, femoral, tibial and dorsalis pedis arteries and popliteal artery was evaluated in prone position. Patients suspected of compression Using linear (6-12MHz) transducer, peripheral arteries evaluated in longitudinal and axial sections in B mode.
Ankle-Brachial Index (ABI): The ABI was performed by measuring the systolic blood pressure from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries after the patient has been at rest in the supine position for 10 minutes. The systolic pressures were recorded with a handheld 5- or 10-mHz .A standard blood pressure cuff can be used at the ankle. As with arm pressures, the most accurate pressure readings were obtained when the blood pressure cuff is appropriately sized to the patient's lower calf (immediately above the ankle).
Carbon Dioxide-enriched Water Bath (CO2 Immersion): Artificial carbon dioxide containing water for foot bathing was generated using Carbothera® (MRE-SPA-MD, Mitsubishi Rayon Engineering, Tokyo, Japan) were dissolved and the concentration of CO2x(free CO2 concentration, 1,000 to 1,200 mg/l, pH 4.6).It can instantly enrich 5 L/min of tap water (pH 6.8) with CO2 Patients recorded the immersion dates, which were confirmed by the investigators. The foot of patients were immersed inxCO2-enriched water (depth of 20–30 cm, 37–38°C, duration for 30 minutes)x3 times per week for the next 3 months[11,12].
Statistical analysis: Descriptive measures and T-test analysis were used to examine associations and differences in Demographic and clinical variables. The significance level for all analyses was set at a probability (P) of less than or equal to 0.05. All analyses will perform by GraphPad Prism 5.3 for Windows (GraphPad Software, San Diego, CA, USA).

III. Results

Demographic Data : according to demographic data there is no significant between CO2 therapy group and traditional therapy group in the age which high %in age between 40-60 (54%and 56%) respectively, according to the sex there is no significant between male and female in the two groups, also there is no significant in physical activity, family history if DM, smoking habit, insulin therapy and BMI , also in hypertension history as mention in (Table 1). According to laboratory investigation there is no significant deference between CO2 therapy group and traditional therapy group in RBS, HbA1c, RFT (Blood Urea, S Creatinine), LFT and lipid profile in the two groups as mention in (Table 2). The Ankle Brachial Index (ABI) study there is No significant changes in Traditional therapy group ,while there is highly significant changes in CO2 therapy group ($P < 0.001$).as shown in (Figure 3.1). In the Doppler study there is No significant changes in Traditional therapy group, while there is high significant changes in CO2 therapy group ($P < 0.01$).as shown in (Figure 3.2) According to the wounds examination, there is no significant changes in traditional therapy group, while dramatic changes in the CO2 therapy group ($P < 0.001$ in size of wound ulcer, $P < 0.001$ in wound color and $P < 0.01$ in wound sensation) as shown in (Figure 3.3) There was no significant difference with no correlation between HbA1c and ABI in post CO2 therapy group ($r = -0.095$, $p = 0.68$) as shown in (Figure 3.4),

also There was no significant difference with no correlation between HbA1c and color and sensation of wound in post CO2 therapy group (r= -o.52, p=0.72; r= -0.032, p=0.823) respectively, as shown in (Figure 3.4) and (Figure 3.4) .There was no significant difference with weak correlation between HbA1c and Doppler study in post CO2 therapy group (r= 0.071, p = 0.623) as shown in (Figure 3.4), also There was no significant difference with weak correlation between HbA1c with size of wound in post CO2 therapy group (r= o.452, p=0.001) as shown in (Figure 3.4).

IV. Figures And Tables

Table 4.1. Demographic variables of patients with CO2 therapy group and with traditional therapy groups

Variables		CO2 therapy (n=50, %)	Traditional Therapy (n=50, %)	*P value*
Age (years)	40-60	27 (54%)	28 (56%)	>0.05
	>60	23 (38%)	22(40%)	>0.05
Age(years)	Mean ± SD	51.6± 8.435	52.92±9.163	>0.05
Sex	Male	31 (59%)	28 (53%)	>0.05
	Female	19 (41%)	22 (47%)	>0.05
Physical Activity	Mild	29 (17%)	32 (44%)	>0.05
	Moderate	21 (83%)	18 (56%)	>0.05
Smoking Habit	Smoker	28 (5%)	30 (31%)	>0.05
	Non-smoker	22(51%)	20 (41%)	>0.05
Hypertension	Hypertensive	36 (88%)	29(66%)	>0.05
	Non-hypertensive	14 (12%)	21(34%)	>0.05
Family history of DM	yes	38 (88%)	41 (66%)	>0.05
	no	12 (12%)	9(34%)	>0.05
Insulin therapy	on insulin	15 (88%)	12 (66%)	>0.05
	on oral medication	35 (12%)	38(34%)	>0.05
BMI (kg/m2)	<25	2 (29%)	3 (33%)	>0.05
	25-30	38 (59%)	36 (39%)	>0.05
	> 30	10 (12%)	11 (28%)	>0.05

(P is significant at <0.05).
(DM: diabetic mellitus, BMI: body mass index).

Table 4.2. Laboratory investigation data of patients with CO2 therapy group and traditional therapy groups.

Laboratory Test	CO2 therapy Mean + SD	Traditional Therapy Mean + SD	*P value*
RBS (mg/dl)	218. 8 + 22.15	224.2+ 31.14	>0.05
HbA1c (%)	8.92+ 0.75	9.56+ 0.76	>0.05
Blood Urea (mg/dl)	38.3 ± 19.5	33.3 ± 12.1	>0.05
Serum Creatinine (mg/dl)	0.80 ± 0.6	0.89 ± 0.38	>0.05
ALT (IU/L)	38.1 ± 16.7	46.1 ± 26.7	>0.05
AST (IU/L)	33.6 ± 14.2	53.6 ± 19.4	*>0.05*
ALP (IU/L)	69.4 ± 19.4	86.4 ± 21.2	>0.05
Total cholesterol (mg/dl)	226.4± 31.1	165.5 ± 26.8	>0.05
Triglyceride (mg/dl)	218.3 ± 49.7	148.3 ± 12.1	*>0.05*
LDL (mg/dl)	171.10 ± 47.50	123.2 ± 41.38	>0.05
HDL (mg/dl)	41.10 ± 7.6	53 ± 9.38	>0.05

(P is significant at <0.05).

(RBS: random blood sugar, HbA1c: glycated hemoglobin, ALT: alanine aminotransferase; AST: aspartate aminotransferase; γ-GT: gamma-glutamyl transferase; ALP: alkaline phosphatase, HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein).

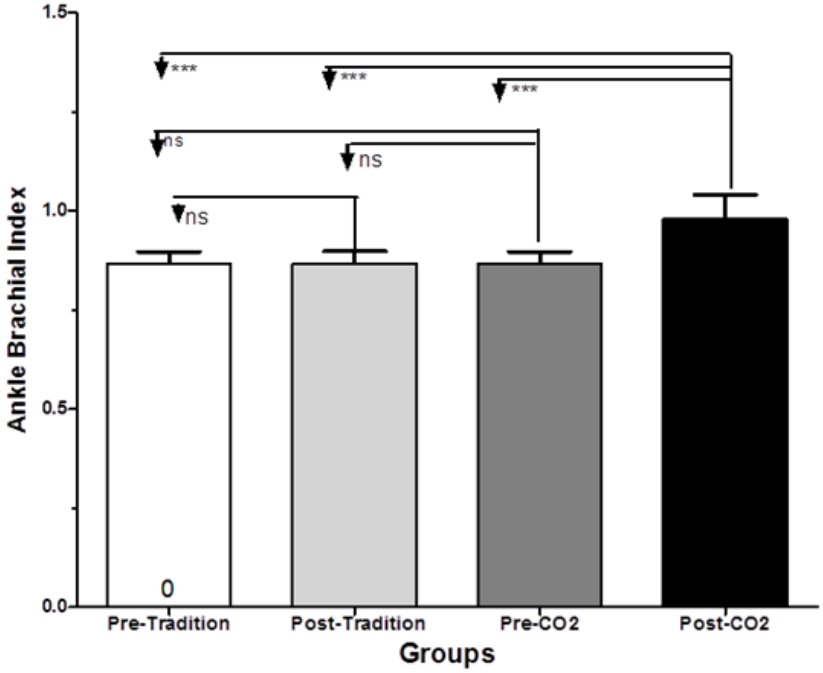

Fig. 3.1. Mean ankle brachial index for pre and post therapy in both groups. The number of asterisks (*) corresponds to the level of statistical significance (*** $p < 0.001$). All values refer to mean ± standard deviation (SD).

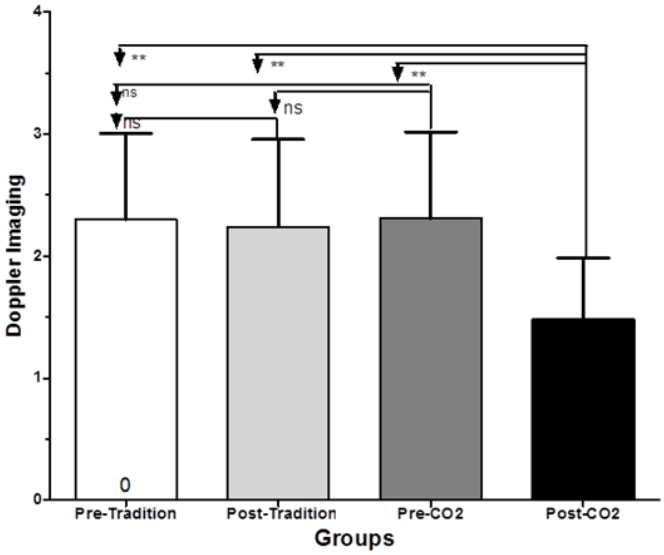

Fig. 3.2. Mean Doppler imaging values for pre and post therapy in both groups. The number of asterisks (*) corresponds to the level of statistical significance (** $p < 0.01$). All values refer to mean ± standard deviation (SD).

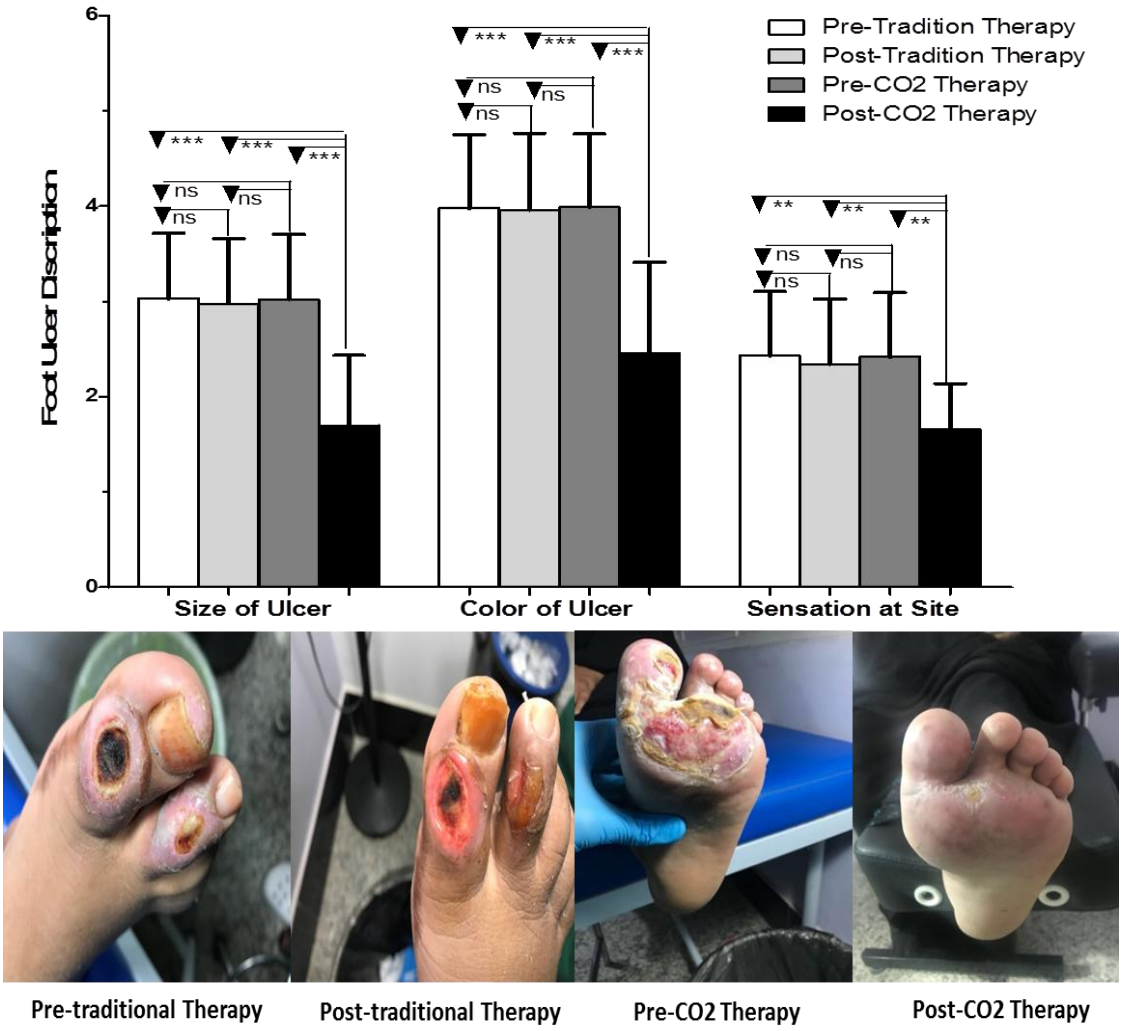

Fig. 3.3. Mean grading of size and color of ulcer and peripheral sensation in pre and post therapy in both groups. The number of asterisks (*) corresponds to the level of statistical significance (** $p < 0.01$, *** $p < 0.001$). All values refer to mean ± standard deviation (SD).

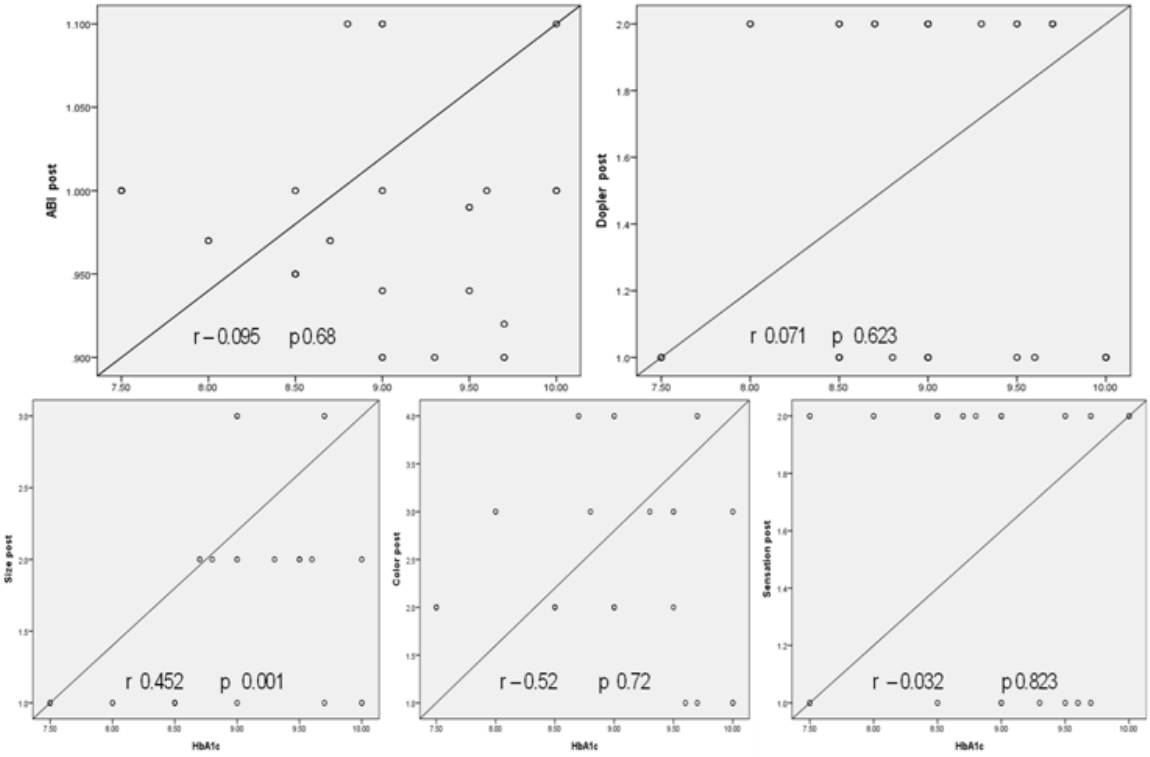

Fig. 3.4. Logistic linear correlation between diabetes and certain parameters(ankle brachial index (ABI), Doppler imaging study, size and color of ulcer and the sensation at site of ulcer) in post carbon dioxide therapy group.

V. Discussion

Patients with different diabetic foot lesion from simple lesion to gangrenous were included. In fact, the benefits of CO2 bathing have been described for the past 50 years, and this therapy is now thought to be effective for the treatment of peripheral vascular disorder[13]. Ankle brachial index has been shown to increase after CO2 bath therapy in CO2 therapy group, which indicates the improvement of endothelial function after CO2 bathing for three month. However, the mechanism or mechanisms underlying this traditional therapy remain poorly defined. The effect of CO2-enriched water on cutaneous circulation depends primarily on the vasodilation elicited by the CO2 that diffuses into the subcutaneous tissue through the skin layers this description seem to be similar to other studies[14,15]. Our results showed that CO2 bathing significantly reduced arterial stiffen, the peripheral arteries of diabetic patients which resulting in increased peripheral blood flow as shown in changes of Doppler reading before and after CO2 bath therapy in patient group, which similar to other studies [12,16]. These observations therefore suggest that CO2 bathing induces peripheral vasodilation and may increase parasympathetic nerve activity or may decrease sympathetic nerve activity as previously described by Toriyama et al[10,11,15], Which similar to our study. Although the mechanisms underlying the effects of CO2 water bathing remain unknown, Diameter changes after an increase in flow depend on the endothelium, mainly through a nitric oxide-dependent mechanism but also through vascular smooth muscle cell contraction and relaxation. Endothelial dysfunction may be considered a cardiovascular risk factor or at least a cardiovascular risk marker[17], but impairment of vascular smooth muscle cell function has also been reported in diabetic patients[16] .The improved circulation induced by carboxy therapy is due to improved tissue oxygenation. The hypercarpnia results in increase oxygen exchange between blood hemoglobin and myoglobuline of the peripheral tissues. It also decreases resistance of the arteries in the skin and muscles, which dilate because of the decline in pH. This differential pH change favors the unloading of oxygen in the tissues making hemoglobin more efficient transporter for oxygen. It also permits the release of growth factor for angiogenesis[18]. Some studies showed that vasodilation is mediated by nitric oxide, which induces angiogenesis and suppresses vasoconstriction in response to cold by keeping the patients' feet warm[19].

Carbon dioxide absorbed percutaneous has peripheral vasodilation effect, a cutaneous blood flow increasing effect, and a warm sensation sustaining effect. This is why it has been employed therapeutically in Europe and elsewhere for centuries[20]. Treatment methods that have commonly been used include vascular reconstruction accompanied by internal treatment[21]. Results also showed that there was highly significant change in the area of the ulceration ($p > 0.5$) after the specified time of therapy and this against the result of 10.

The cutaneous blood flow was accompanied by a reddening, or flushing, of the skin in immersed areas and by a change in subjective symptoms (Sensation of warmth). The skin flushing effect in a carbon dioxide footbath shows concentration dependence, and is thought to arise from the dilation of precapillary arterioles and capillaries. In addition, Komoto et al. have reported a rise in oxygen partial pressure, both in the skin and muscles, from carbon dioxide adaptation to the skin which is similar to[22,10]. The only data collected in the present study was a rise in cutaneous blood flow, but because these results were indicative of efficacy in ischemic feet, carbon dioxide bathing can certainly be expected to have desirable effects on the skin and muscles of ischemic feet as the study of Shalan,et al.

VI. Conclusion:

Significantly increased cutaneous blood flow in ischemic feet, and improved subjective symptoms. Moreover, the artificial carbon dioxide footbath induced rise in cutaneous blood flow in the feet was found to be reproducible. The same was true of the improvement in subjective symptoms. These results demonstrate the effectiveness of this method in the treatment of ischemic feet, and indicates it is potential utility as a form of physiotherapy in the treatment of ischemic feet. Further studies need to be carried out on related topics, including optimum carbon dioxide concentration and the general effects of carbon dioxide foot bathing on the body.

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