Sclerotherapy using air- or CO_2-O_2-foam*

Post-approval study

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Keywords
CO_2-O_2–Foam-Sclerotherapy, Air-Foam-Sclerotherapy, Efficiency, Side-effects, Visual side-effects

Summary
Objectives and Implementation: This observational study (OS) documented the efficacy and side-effects of ultrasound-guided polidocanol foam sclerotherapy (FS) for air and carbon dioxide/dioxygen foam sclerotherapy (CO_2-O_2 FS) through the use of an internet-based protocol. The patients were included in the study; two centers have consequently treated all their patients with CO_2-O_2 FS.
Materials and Methods: Eleven centers participated in this OS, nine centers worked with air-based FS, two with CO_2-O_2 FS. Only approved drugs were used. With 376 patients in 553 treatments, air-based FS was performed using 0.25 % to 4 % polidocanol microfoam (Aethoxysklerol®, Kreussler). 125 patients in 152 sessions were treated with CO_2-O_2-based foam using 1 % to 3 % polidocanol with seven parts CO_2 (Laparox®, Linde) to three parts O_2 (Conoxia®, Linde). For the sterile dispensing of the CO_2-O_2 FS a mass flow controller was used. A final clinical examination and ultrasonic testing followed four to six weeks after the last therapy session.
Results: Varicose veins larger than 3 mm were treated with an average of 5.3ml in the air-FS and 8.2 ml in the CO_2-O_2 FS, significant p<.0001.
Side-effects with – Hyperpigmentation: air: 23.3 %, CO_2-O_2: 13.6 %. – Hematoma: air 14.4 %, CO_2-O_2: 2.5 %. – Migrane: air: 0.1 %, CO_2-O_2: none. – Matting: air: 1.4 %, CO_2-O_2: none. – Burning: air: 11.7 %, CO_2-O_2: 5.5 %. – Thrombosis: air: 1.1 %, CO_2-O_2: 1.6 %. – Visual impairment: air: 0,2 % , CO_2-O_2: 2,0 %.
There were no differences between the groups when smaller amounts of foam were used in the air-FS. Topical side-effects were smaller in the group using CO_2-O_2. Treatment was more efficient in that group, because larger volumes could be applied safely. Neither group showed any side effects to the central nervous system; all instances of impaired vision were spontaneously reversible within 20 minutes without further treatment. The findings published here accord with records from over 1000 treatments with CO_2-O_2 FS. With CO_2-O_2 FS there were no incidences of strokes or transient ischemic attacks (TIA). It seems that the treatment with CO_2-O_2 FS is more efficient for larger varicose veins than air FS. The use of physiological gas in foam sclerotherapy is probably safer, but this is not yet proven, and care has always to be taken concerning iatrogenic gas embolism.

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Pathological changes in the venous system of the legs affect more than 80% of the Western population (52). Inexpensive and minimally invasive treatment options that are both highly efficient and safe, are therefore of great therapeutic importance. Foam sclerotherapy monitored by duplex sonography presents a considerable advancement, as pointed out by De Maeseneer (44) in her comment, even though foam sclerotherapy of saphenous veins has a recanalization rate after one year that is three times higher (16.3 %) than that of surgical stripping (4.8%) (58).

For the evaluation of these findings we looked at studies and meta-analyses from Medline via PubMed, Clinical Queries, Cochrane, from 1993 onward, with the following contents: Comparison of more than two treatment methods (liquid sclerotherapy, foam sclerotherapy with air, foam sclerotherapy with other gases). We also looked at reports of complications using these therapies with polidocanol or sodium tetradecyl sulphate (STS), in liquid or foam form. The gas mixture with 70 % CO_2 and 30 % O_2 is based on the work of Cavezzi (10), which ensures the foam with polidocanol (Aethoxysclerol®, Kreussler) is sufficiently stable for foam sclerotherapy (FS).

The authors assessed the validity of the selected studies according to methodology and outcome. This literature was used for assessment and comparison with the results presented here. Between 1994 and 2004, four strokes and one transient ischemic attack (TIA) were recorded after scleroses of varicose veins with liquid polidocanol and other sclerosing agents (15, 34, 38, 53, 55). Since 2006, ten strokes and eight transient ischemic attacks have been associated with air foam sclerotherapy as published in the work of Parsi (53).

The number of TIAs of only a few minutes in duration , at 0.9 %, is surely not adequately represented in the literature (35, 62). The authors have come across, but not published, several such cases when administering air foam- sclerotherapy, and have been told of similar incidents reported by colleagues in person. That statement obviously does not apply to this observational study.

* The English version is only available online.

Patients and Methods

This non-interventional trial in accordance with the terms of § 4–3, and § 23–3 German Drug Registration and Administration Act (AMG) and § 23 Medical Devices Act (MPG) intends to collect new evidence on the effectiveness and safety of sclerotherapy for varicose veins by means of drugs (sclero-therapeutics) and medical devices (compression). The findings are to be collected in a 'registry' – all within the authorized indication and under the conditions of routine medical application.

This analysis investigates variations of the therapy that differ by the type of sclerotherapy (air vs. CO_2-O_2) and compression (used or not). The observational study should bring about new findings of known adverse drug reactions (ADRs) under routine use (assessment of severity, frequency estimation, interactions).

Outcome parameters

Primary efficacy objectives:
- effectiveness (of the sclerotherapy-foam) with and without compression

Primary safety objectives:
- acute complications after sclerotherapy
- medium-term complications and side effects after sclerotherapy
- number of incisions

Secondary objectives:
- effectiveness of sclerotherapy depending on the localization of varicose veins

Design of Study

In this project the special aspects of sclerotherapy with air or CO_2-O_2–foam using polidocanol (Aethoxysclerol®) were investigated. An electronic case report form on the internet was used .

During the first round, general patient-related data (CEAP (19)) were obtained and the first sclerotherapy session conducted.

After two weeks during the second round , the result of the first sclerotherapy session was logged (including any ADRs) and if necessary further sclerotherapy sessions were carried out.

Third round as second.

The fourth session is the final check, about 6 weeks after the last sclerotherapy session.

Patients with the following types of varicose veins with a diameter >3mm were treated and evaluated:

the great saphenous vein (GSV) and small saphenous vein (SSV), recurrent varicose veins and varicose side branches. The compression was performed immediately after sclerotherapy with either dual-tension compression bandages for 1 to 2 days, or with compression stockings (calf or thigh) Class 2 compression, wearing time 1–3 weeks (▶Tab. 1).

Exclusion criteria:

- known allergy to the sclerosing agents or severe allergic diathesis
- symptomatic atrial septal defect
- previous neurological complications due to foam sclerotherapy
- severe systemic disease
- febrile states
- inflammatory skin diseases
- acute superficial or deep vein thrombosis
- infections, either located in the area of the performed sclerotherapy or severe, general infections
- immobility
- bedridden
- advanced arterial occlusive disease stages II to IV
- pregnancy, nursing period, or desire to become pregnant
- long-term diabetic complications (e.g. polyneuropathy)
- peripheral vascular disease (Ankle Brachial Pressure Index <0.8)
- poor general state of health
- bronchial asthma
- known thrombophilia
- thrombophilia after acute deep vein thrombosis
- known thrombophilic diathesis
- recovering alcoholics (Aethoxysclerol® preparations contain 5 % alcohol)
- participation in a clinical trial within the last 4 weeks.

A previously known asymptomatic atrial septal defect was not considered a contraindication.

Time Table

The observation period for each patient was determined by the number of necessary sclerotherapy sessions which varied from six weeks (after one session) to up to 10 weeks (three sessions)

Quality Control Measures

The success of sclerotherapy was defined by the following duplex controlled criteria :
- **Excellent**: sclerotherapy complete, no lumen in the sclerotherapy area shows up during duplex ultrasonography.
- **Good**: thrombus and residual lumen detected in the sclerotherapy area. During

Tab. 1 CEAP classification of the patients treated by foam categories.

CEAP	Air-foam		CO_2/O_2-foam		Total
	N	%	N	%	N
C2 (>3 mm)	320	85.7	76	61.4	396
C3	35	9	15	12	50
C4a	12	3.2	15	12	27
C4b	2	0.4	12	9	14
C5	3	0.7	3	2.4	6
C6	4	1.0	4	3.2	8
Total	376	100	125	100	501

Tab. 2 Mixture ratio of air, foam and liquid volumes (in ml).

Liquid/air	Volume Air foam					Volume CO_2-O_2-foam					
	mean	StD	min	max	n	mean	StD	min	max	n	p-value
1+3	4.8	1.0	4.0	6.0	4	3.6	2.1	1.0	6.0	4	0.5147
1+4	5.2	2.8	0.5	18.0	539	7.6	4.0	1.5	20.0	110	<0.0001
1+5	8.2	4.2	1.0	15.0	10	8.8	4.4	2.0	20.0	38	0.8604

Tab. 3 Concentrations of foam used. (GSV: great saphenous vein; SSV: small saphenous vein; VSB: varicose side branches; RVA: Recurrent varicose veins)

Polidocanol concentrations		VSM		VSP		Both		VSB/RVA		Total
		N	%	N	%	N	%	N	%	N
Air foam	0,5%	1	0.3	1	1.4	-	-	10	8.1	12
	1,0%	29	8.6	6	8.6	1	4.5	28	22.8	64
	2,0%	19	5.6	3	4.3	-	-	24	19.5	46
	3,0%	286	84.6	60	85.7	21	95.5	59	48.0	426
	4,0%	3	0.9	-	-	-	-	-	-	3
	Other	-	-	-	-	-	-	2	1.6	2
	Total	338	100	70	100	22	100	123	100	553
CO_2-O_2-foam	0,5%	-	-	-	-	-	-	-	-	-
	1,0%	1	3.8	-	-	-	-	28	24.3	29
	2,0%	4	15.4	2	18.2	-	-	62	53.9	68
	3,0%	21	80.8	9	81.8	-	-	22	19.1	52
	4,0%	-	-	-	-	-	-	-	-	-
	Other							3	2.6	3
	Total	26	100	11	100	-	-	115	100	152

VSM: Vena saphena magna, VSP: Vena saphena parva, VSB: Varicose side branches, RVA: Recurrent Varicosis, Other: Polidocanol 1,5% mit NaCl 0,9%

the duplex ultrasonography the residual lumen shows no venous flow.

- **Moderate**: partially thrombosed, duplex ultrasonography shows flow in the sclerosed area
- **No improvement**: veins open as before
- **Worse**: veins remain open, pigmentation, periphlebitis

The polidocanol foam sclerotherapy (PFS) was carried out mainly with polidocanol 3% (0.5% to 4% Aethoxysclerol®, Kreussler). Foam creation: liquid/gas ratio 4 to 1. The air group also used foam with 0.5% polidocanol whereas no mixture with gas was used in the CO_2-O_2 group (▶Tab. 2, ▶Tab. 3).

Equipment

Starting from the patented application DE 198 12 551 C2 (developed by Dr. Jakob Hoiss), we developed a device to fill sterile syringes with gas mixtures in a sterile environment. The device was built by Dr. Hoiss: Schico high-accuracy gas dispenser M2000DUO; the patent number issued by the German Patent and Trademark Office (DPMA) is 10 2009 037 765.

The object of the new method of gas-preparation is that the foam sclerotherapy presents reduced risks for doctor and patient. Either by way of a mass flow measuring technique based on hot film anemometry, or through two appropriately arranged valves, at least two gases are mixed and filled into the syringe under sterile conditions. The ratio of this gas mixture can be adjusted according to need.

Polidocanol foam with pure CO_2 decays twice as fast as after making a foam mixture with CO_2-O_2 in the ratio 70:30 as described by Cavezzi (10). The previous use of regular air and the nitrogen that comes with it and which is poorly soluble in the body (36) has been replaced with the easily soluable, clinically approved CO_2 (17) in combination with O_2 (10).

▶Figure 1 shows the apparatus for mass flow measurement that allows the individualized composition of different gases. In-vivo studies with 12-MHz ultrasonography have shown that the intravenous bubbles of FS using CO_2-O_2 foam are smaller than the bubbles of the foam in air-FS. The CO_2-O_2 gas mixture at a ratio of 70:30 has been pro-

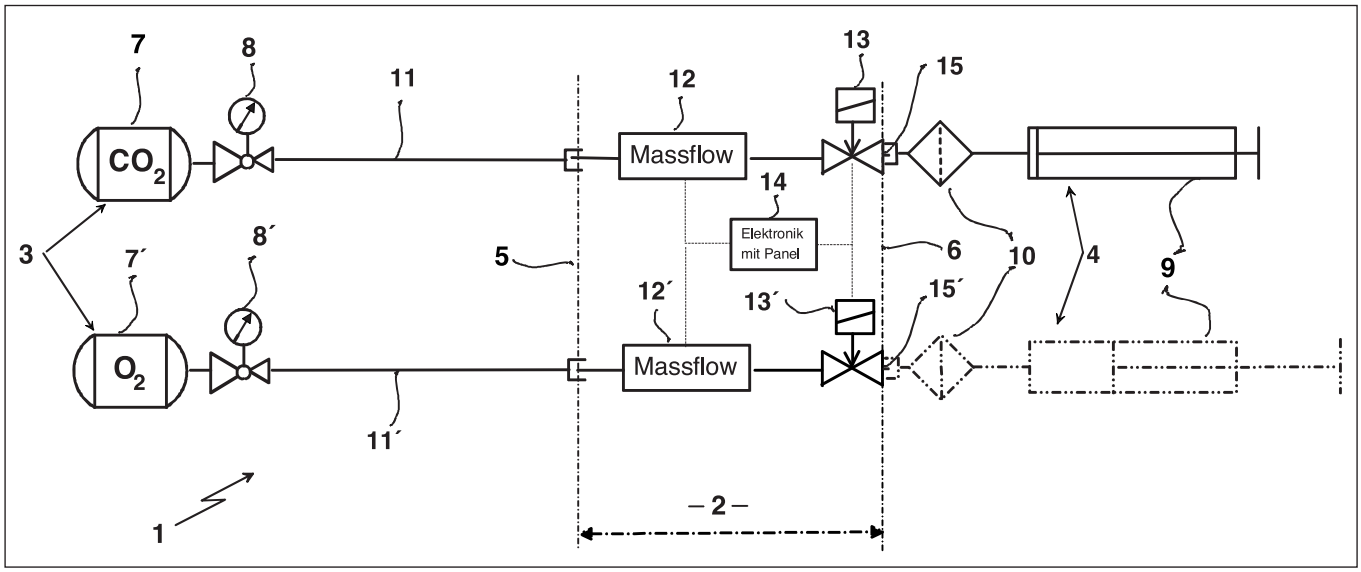

Fig. 1 High-accuracy gas dispenser M2000 Duo (1 apparatus for the production of a CO2-O2 mixture; 2 portable container; 3 unit impinging the container; 4 unit impinging the container; 5 input side 3; 6 output side 4; 7 ,7′ pressure tank; 8, 8′ Reducing valve with manometer; 9 syringe; 10 filter; 11, 11′ line system; 12, 12′ Mass flow measurement systems; 13, 13′ control valve; 14 Electronic part with panel; 15, 15′ outlet).

ven as the most effective ratio for patient treatment, because the foam is sufficiently stable for the FS (10, 69).

For the local production and use of the CO_2-O_2 gas mixture, the apparatus is mounted in a transportable container (▶Fig. 2). Sterile detachment of units on both ends of the container is always possible. The device is subject to the European Medical Device Directive (MDD).

Our own gas chromatography measurements (lab of Dr. Graner & Partners, 81249 Munich) showed that usage of the M2000duo left only about 1.5% residual nitrogen N_2. (Report 101839 B, 04.XII.2010) For the protocols see ▶Figure 3. The apparatus' instructions must be observed carefully when handling connections, the apparatus, and filling the syringes. If the plugs were left off for just two minutes while the syringes were filled, the nitrogen content immediately increasd to 3%. Even with the syringe closed, the nitrogen content increased by 3 volume percent per 24 hours of storage.

Failing to rinse the system properly before filling the syringe increased the N_2 concentration to approximately 20 %. After changing the gas canisters and after prolonged idleness (i.e. after the weekend), both gas pipelines had to be rinsed for three minutes. The same three-minute rinsing also had to be undertaken every time before filling gases into the syringes. Five and ten ml syringes (Omnifix®) were used for this.

The syringes were attached to a new 0.2µm filter, while the gas was emanating from the connector. The syringes were first filled to 80 % with oxygen and then immediately sealed with a sterile plastic plug. Then the switch to the CO_2 connection was made, attaching the syringes again while the gas was emanating from the connector. Right before attaching to the CO_2-valve, the oxygen in the 10 ml syringe was ejected until 3 ml were left; in the 5 ml syringe the oxygen was reduced to 1.5 ml. The syringes were then filled with CO_2 to 10, respectively 5 ml. Immediately thereafter, the syringes were closed with dead end caps. It was imperative to ensure that the connections from apparatus to filter and to the syringe fit tightly. The same goes for the plug. The syringes were then marked with the date of filling and could be used during the remaining day.

The pressure cylinders connected to the appartus (medical carbon dioxide CO_2 Laparox®; medical oxygen O_2 Conoxia®, both from Linde) (41) were left open during the

Fig. 2 High-accuracy gas dispenser M2000 Duo with sterile filter and syringe.

work week, so that the device was always under positive pressure.

Foaming of the gas was carried out in accordance with the DSS Tessari technique, using a sterile female-female adapter as described in Breu (6). The concentrations of polidocanol (Aethoxysclerol®) used were between 1 and 3 %, the ratio of liquid to gas was 1 + 4.

The CO_2-O_2-polidocanol foam (polidocanol 1–3 %) was injected under sonographical control, in quantities of up to 20 ml per session. The application with these quantities followed the recommendations of Morrison (47). The foam quantities are approximately twice as large as the amounts recommended by Breu (6) who suggests 10 ml per session. **The recommendations of Breu (6) apply to polidocanol-air foam.** In the observational study extensive pathologies were efficiently treated within 1–3 sclerotherapy sessions.

The observational study for sclerotherapy with air or the above-mentioned CO_2-O_2-mixture was conducted via an online registry of the sclerotherapy work group of the Deutsche Gesellschaft für Phlebology (DGP, German Phleobology Society), and approval of the Ethics Committee of the Medical Association of Baden-Wuerttemberg, file no. 2007–119.f. The observational studies in the medical practice of the Sclerotherapy Work Group of the DGP followed the protocol-skl 01 Version 1.1, 06.II.2008.

Heads of the clinical trial were Dr. Karsten Hartmann (coordination), Zähringerstr. 14, 79108 Freiburg and Dr. Franz Xaver Breu, Tegernsee Str 101, 83700 Rottach-Egern.

The use of polidocanol foam was approved by the Federal Institute for Drugs and Medical Devices (BfArM) in October of 2009.

Statistics

Online registration and statistical analysis was handled by Dr. Eike G. Fischer, Aix Scientifics® CRO, Pauwelsstrasse 19 (MTZ), D–52074 Aachen, eike@aix-scientifics.com (http://aix-scientifics.com). The statistical calculation of the significance was performed using the Wilcoxon-Mann Whitney-Test.

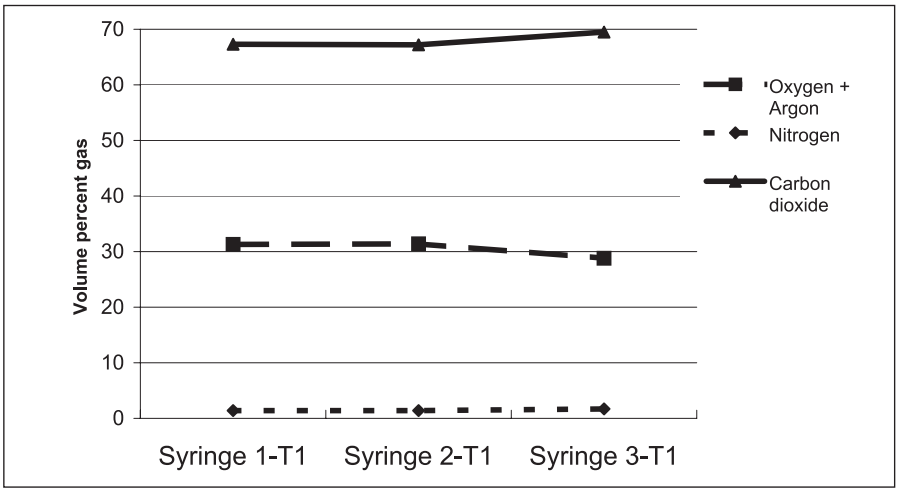

Fig. 3 Report 1018390B – 01.12.2010 with lock after filling with CO_2 and O_2, chart with 3 data series.

Results

501 patients, of whom 430 were women (70.2 %) and 171 men (29.1%), were treated with foam sclerotherapy either using air or CO_2-O_2 foam , a significant difference (p<.0001), which occurred equally often in both treatment groups. 376 patients received 553 treatments with air-foam; 125 patients were registered as having been treated with 152 CO_2-O_2-based foam sessions. Most treatments took place at the CEAP C2 stage (▶Tab. 1). In the group treated with air-based foam, 73.8 % had saphenous veins treated; in 26.2 % of the cases varicose side branches and recurrent varicose veins were sclerosed. For the group treated with CO_2-O_2-based foam the distribution was 24.4 % GSV to 75.6 % for treatment of varicose side branches and recurrent varicose veins respectively (▶Tab. 3).

The average age of the women in the air and CO_2-O_2 groups was 55.6 and 58,5 years, respectively that of the men 59.4 and 63,4 – no significant differences between the two groups.

The body mass index (BMI) didn't significantly diverge between the two groups either; with an average of 25.4 for the women and 26.9 for the men.

In the CO_2-O_2 group compression therapy was performed in 97.6 % of the cases, in the air group and in 75.2 % significant with a p of 0.01

The complete closure of **atrophied varicose veins** was (▶Tab. 4):

- *Very good* in the group treated with air foam in 82,7 % of the cases and in 87,3 % of the cases in the in the CO_2-O_2 group.
- *Good* in the air group in 9,7% of the cases, and 9,1% of the cases in the CO_2-O_2 group.
- *Moderate* in the 4,0 % of the cases in the air group and 3,6 % of the cases in the CO_2-O_2 group.
- *No change* in the 3,6 % of the cases in the air group and 0 % of the cases in the CO_2-O_2 group.

Tab. 4 Effectiveness rating of the physician per given treatment.

Evaluation	Air foam		CO_2-O_2-foam	
	N	%	N	%
very good	457	82.7	133	87.3
good	54	9.7	14	9.1
moderate	22	4,0	5	3.6
no change	20	3.6	-	-
Total	553	100	152	100

The closure rate was not significant different between air and CO_2-O_2 foam.

The highest rate of very good results was detected in the CO_2-O_2 group when using 3% polidocanol foam (p=0.05). In the air group patients best responded to treatment with 2% polidocanol foam, no significant difference in the air group (▶Tab. 5). Because these particular criteria were included in the internet form only later on, the numbers of patients per treatment are lower than in the other tables.

The amount of sclerotherapy foam used in the CO_2-O_2 group—throughout all treatment groups (Recurrent varicose veins, varicose side branches, GSV, SSV)—exceeded that of the amount administered by the air group by 64%: 5.3 ± 2.8 ml for air and 8.2 ± 4.2 ml for CO_2-O_2 – a significant difference (p<.0001) in all groups.

Microthrombi as an expression of sclerotherapy activity was documented in the air group with 3.5% in the CO_2-O_2 group were significantly more frequent at 72.9% (p<0.0001).

Mini-incison either by scalpel or by a needle were made in 26.4% of the cases in the the air group, and in 43.6%. of those the CO_2-O_2 group. A needle was used in the air group in 73.3% of the cases, and a scalpel in the CO_2-O_2 group in 84.8% of the cases.

Tab. 5 Foam-effectiveness rating of the physician.

Polidocanol-Konzentration		Air		CO_2-O_2	
		N	%	N	%
0.5%	**very good**	5	62.5	-	-
	good	3	37.5	-	-
	moderate	-	-	-	-
	no change	-	-	-	-
	Total	**8**	**100**	**-**	**-**
1.0%	very good	48	88.9	19	73.1
	good	5	9.3	6	23.1
	moderate	1	1.9	1	3.8
	no change	-	-	-	-
	Total	**54**	**100**	**26**	**100**
2.0%	very good	32	94.1	48	88.9
	good	2	5.9	4	7.4
	moderate	-	-	2	3.7
	no change	-	-	-	-
	Total	**34**	**100**	**54**	**100**
3.0%	very good	308	81.5	34	91.9
	good	36	9.5	3	8.1
	moderate	17	4.5	-	-
	no change	17	4.5	-	-
	Total	**378**	**100**	**37**	**100**
4.0%	very good	-	-	-	-
	good	2	66.7	-	-
	moderate	1	33.3	-	-
	no change	-	-	-	-
	Total	**3**	**100**	**-**	**-**

Side effects

Hyperpigmentations occurred significantly more often in the air group (23.3%) than than in the CO_2-O_2 group, at 13.6%, significant at p<.0001.

The same goes for the formation of hematoma after sclerotherapy, which occurred in 14.4% of the cases in the air group, and in the CO_2-O_2 group in 2.5%, significant with p<.0001.

The following side effects were not seen in the CO_2-O_2 and rarely occurred in the air group: itching:1.1%, necrosis of the skin: 0.3%, migraine: 0.1%. Telangiectasia/matting were observed in the air group in 1.4% of the cases, and not at all in the CO_2-O_2 group. Burning sensation during the injection was noted in 11.7% of the cases in the in the air group, and among 5.5% of the CO_2-O_2.

Occurence of the following side effects was comparable in both groups: Post-injection pain: 2.6% when air foam was used, 2.5% for CO_2-O_2-foam. Ascending phlebitis: 5,4% in the air group, 2,6% CO_2-O_2 group. Deep vein Thromboses: 1.1% in the air group (including one pelvic venous thrombosis) and 1.6% in the CO_2-O_2 group (two calf muscle vein thromboses, one of them in the contralateral, untreated leg).

Because failure to rinse the system properly before filling the syringe increased the N_2 concentration to approximately 20%, there were two occurances of visual impairment during the early stage of the observational study, both of them completely reversible within 10 to 25 minutes.

During foam sclerotherapy with up to 1.5% residual nitrogen using 6ml CO_2-O_2 2% Polidocanol foam there was one case of visual impairment. In that case a popliteal perforating varicose side branches was sclerosed. The visual impairment receded spontaneously and completely after 20 minutes. The subsequent investigation revealed a small meningioma, a migraine, no atrial septal defect.

Visual impairment in either groups was always temporary and always went away completely within one to 20 minutes. No neurological changes could be found in control check-ups.

Frequency of visual impairment: Air group 0.2%, CO_2-O_2 group 2.0% (p= 0.0392, n.s.).

Considerable sensation of tightness in the chest for 10 minutes was documented once in the CO_2-O_2 group (8 ml of 2 % Polidocanol foam, 1+4). There was no occurance of that in the air group. In the CO_2-O_2 group one case occurred four weeks after sclerotherapy of the GSV, where a 84-year-old female patient (CEAP C6) experienced a hematoma to the brain stem. A connection with the treatment is unlikely.

Discussion

On the methods

This observational study was initiated by the principal investigators (PI) themselves. It seems fair to assume that the PIs were very keen to enter correct data, which is why monitoring was not deemed necessary. Each PI was asked, as far as possible, to have the data input checked by a second person within its medical center (or doctor's office). This second person also received right of access to the data. In this observational study, the medically approved sterile physiological gases have been examined in the applicability of sclerotherapy foam for the first time.

The amounts of foam used in the air group conformed to those applied by Ceulen (11), Gillet (23) and Yamaki (72) and were approximately twice as high as in the study of Hamahata (32). Beckitt (2) used equal amounts of foam of STS-air-foam and STS-CO_2-O_2-foam , that result was matched by our CO_2-O_2 group using comparable amounts of foam as Beckitt (2).

According to Eckman (18) the advantage of polidocanol foam with CO_2-O_2 is that its bubbles are more rapidly absorbable and smaller compared to polidocanol foam with 80% N_2 (plain air). Eckmann's study (18) also shows that CO_2 polidocanol foam blocks fewer small capillaries. Whether this means any advantage in clinical application, studies have yet to show (22).

We were able to verify the smaller size of the bubbles in vivo (through ultrasonography) and in vitro in studies of our own (▶Fig. 3). In 200 x magnification it is easy to see that the bubbles in polidocanol foam with CO_2-O_2 are smaller than in air foam (see▶Figure 4) . This applied to polidocanol concentrations from 0.5% to 3%. Cavezzi (10) and Wollmann (69) have published on the theoretical foundations of sclerotherapy-foam in vessels with different gases.

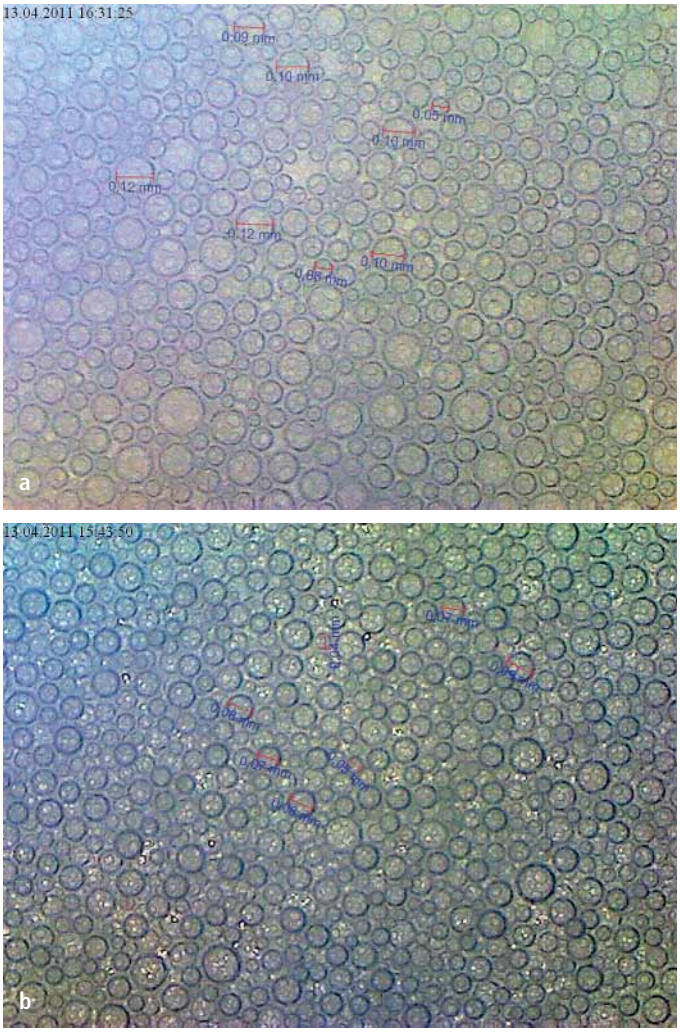

Fig. 4
Bubble size in vitro after 1 min, magnification 200x (a. Polidocanol 1% air-foam, b. Polidocanol 1% CO_2-O_2-foam).

Since Morrison's work (45, 47), sclerotherapy with air no longer seems desirable, because adverse effects, at least at high foam volumes, occured three times more frequently than after CO_2-O_2 FS (using a 70–30 ratio and a composition of one part liquid plus 4 parts gas). These difference were not significant, because the number of cases was too small. Hlastala (37) has worked in vitro on the associated pathophysiology of the intravascular behavior of air-foam.

In an FDA-approved study (60) with CO_2-O_2-foam (Varisolve®), 82 patients were treated with up to 24 ml of Varisolve®, and there were no serious complications (neurological, ophthalmologic, MR before/after treatment). Only one case of visual impairment of 20 seconds duration occurred, even though 65 patients showed a right-to-left cardiac shunt in asymptomatic atrial septal defects when performing valsalva maneuvers. Foam bubbles in the middle cerebral artery were detected in 60 patients (60).

Varisolve® with an ultra-low amount of 0.8 % N_2 seems comparable to the presented gas mixture with a residual nitrogen content of 1.5 %, fabricated with this new method of gas-preparation for the CO_2-O_2 FS. Varisolve® is close to FDA approval in the U.S. (1.60). Earlier studies (17, 36) and the data of Morrison (46) led to the green-lighting of the FS using CO_2-O_2 when atrial septal defects were present. This raises the question whether it might not be better to work with CO_2-O_2 in all cases, given that

intrapulmonary shunting (64, 66, 68) is a regular occurrence. This has not yet been studied in comments about the safety of FS (2–4, 43, 51).

With the new method of gas fine dosing, there were no technical difficulties. Larger amounts of CO_2-O_2-foam meant that treatments were more efficient and had signicantly fewer local side effects, see below.

On the effectiveness

This CO_2-O_2 group, together with the publications of Beckitt (2), Morrison (47), Regan (60), Wright (70) worked with an average of 13.5 ml of foam. This is twice as much as the literature indicates for air foam, which is 6.1 ml for the foam sclerotherapy with air (2, 5, 17, 25, 29, 32, 33, 50, 51, 56). This means that according to the literature and as a result of this observational study, a more intensive foam sclerotherapy with CO_2-O_2 foam is possible without significantly increased side effects, as will be discussed further below. Our observational study shows this to be true for varicose veins 3 mm in diameter and larger.

Polidocanol foam is more stable at higher concentrations (16, 69), which presumably results in smoother endothelial damage. What is striking about this observational study (OS) is that both groups worked with higher concentrations of polidocanol in the foam than other groups have (27, 28, 56) . The response to treatment was better in this OS with higher polidocanol CO_2-O_2 foam concentrations (borderline significance, p0,05, in the air group the difference was not significant).

The CO_2-O_2 group treated saphenous veins in 24.4 % of the cases and varicose side branches and recurrent varicose veins in 75.6 %. In the air group the distrubtion was 73.8 % saphenous veins to 26.2 % of varicose side branches and recurrent varicose veins. When treating GSV and SSV, in more than 80 % of the cases both groups worked with 3% polidocanol foam. Varicose side branches and recurrent varicose veins were predominantly treated with 3 % polidocanol foam by the air group (▶Tab. 5), and with 2 % polidocanol foam by the CO_2-O_2 group.

Still, in all variants of application, the success rate in the CO_2-O_2 group was slightly higher than in the air group, which is either due to the increased amount of foam or the more intense surface interaction on the endothelium of the smaller bubbles in the polidocanol foam. To date, there are no further studies that have looked at this particular aspect. Beckitt (2), too, observed a greater efficacy for STS-CO_2-O_2-foam compared to STS-air foam. Many questions about the mechanisms of polidocanol foam remain yet to be investigated (16). Compression therapy was carried out in the CO_2-O_2 group slightly increased (significant p 0.01), this may explain the difference in frequency of hematomas in the two groups.

The best response (▶Tab. 5) in the CO_2-O_2 group was with 3 % polidocanol-foam; in the air group with 2 % polidocanol-foam. The CO_2-O_2 group showed an increase in the assessed as very good response rates with the higher concentrations of polidocanol (p=0.05).

Hamahata (32) has recorded a good response to the small amounts of foam where he used only 1.5 to 2.5 ml of polidocanol-air-foam on 138 legs and had a similar response as did our air-foam group with 376 patients and 553 treatments using an average of 5.3 ml of foam. Since in both of the studies with these small amounts of air foam neither TIAs and nor strokes occurred, and since the occurrence of thromboses was low (see below) it is worth considering whether the maximum amount of air foam might not be lowered from 10 ml to 5 ml.

Raymond-Martinbeau (59), however, points out that the lower volumes with Hamahata (32) let to a higher recurrence rate and thus poorer long term outcomes. Colerdige Smith (12, 13), too, advised that the necessary volume of foam in the FS is not determinate. Wright (70) reports that the effectiveness with Varisolve 1 % (with an unknown concentration of CO_2-O_2 and an average of 24.9 ml foam was surprisingly low at 68.2 % when compared to the procedure of stripping the GSV. Better results in the same study (70) were achieved by the sclerotherapy group using Varisolve 1 % (on average 14.9 ml foam), where the response rate was 93.8 %. That compares to a response rate of 88 % with the use of self-produced polidocanol-, STS- foam. The working group (70) explains this surprising difference with the fact that the first group had surgeons perform the sclerotherapy, while experienced sclerotherapists were at work in the second group. But why the larger amount of foam was so considerably less effective, is still not explained. In summary, Wright reached (70) a response rate of 83.4 % in this study, a value slightly exceeded by the 85.6 % of the CO_2-O_2 group within our OS.

The OS showed that CO_2-O_2-FS can be used with significantly larger quantities (▶Tab. 6). The effectiveness increases with higher concentrations of polidocanol in the CO_2-O_2-group. The effectiveness of the air-FS and FS-CO_2-O_2 is consistent with the comparative data from the literature. These results show that the different fabricated foams have a virtually identical effect(60, 70 and our data). De Maesener's (44) claim of a 'foam-revolution' is justified, because the extraordinary efficiency compared to liquid sclerotherapy in the treatment of in the treatment of varicose side branches is a great gain.

On the side effects

The presence of hyperpigmentation in our air-foam group was, at 23.3 %, comparable with that in the literature both for STS-foam at 35 % (51) and also for 3 % polidocanol foam at 28.2% in Ceulen (11) and 17.8 % in Jia (29). In our CO_2-O_2 group, hyperpigmentation was further reduced to 13.6 %. In Beckitt (2) the number of hyperpigmentation was also halved in the CO_2-O_2 group to 3.3 %. Their lower hyperpigmentation rate (2) than that of our CO_2-O_2 group is explained by the fact that our group treated 78 % of superficial varicose side branches but Beckitt (2) 86 % deeper lying GSV and SSV.

The decreased hyperpigmentation after sclerotherapy in Beckitt (2) was independent of the number of occurences of phlebitis. These were higher with air foam (5.4 %) than with CO_2-O_2 foam (2,6 %). Ceulen (11), using 3% polidocanol foam had occurrences of thrombophlebitis in 50 %, but presumably equated thrombophlebitis with the desired result from sclerotherapy.

Tab. 6 Foam volume in ml. (GSV: great saphenous vein, SSV: small saphenous vein; VSB: varicose side branches; RVA: Recurrent varicose veins)

VEIN	Volume Air foam					Volume CO_2-O_2-foam					
	mean	StD	min	max	n	mean	StD	min	max	n	P-value
VSB/RVA	5.9	3.2	1.0	18.0	123	8.2	4.4	1.5	20.0	115	<0.0001
VSM	5.6	2.7	0.5	11.0	338	8.7	3.3	3.0	16.0	26	<0.0001
VPA	2.9	1.5	1.0	8.0	70	6.6	3.6	3.0	13.0	11	<0.0001
VSM/VPA	5.0	3.1	1.0	10.0	22						
Total	5.3	2.8	0.5	18.0	553	8.2	4.2	1.5	20.0	152	<0.0001

VSM: Vena saphena magna; VSP: Vena saphena parva; VSB: Varicose side branches; RVA: Recurrent varicosis

Occurrence of ulcerations after sclerotherapy in our air group was at 0.2 %, none occurred in the CO_2-O_2 group. MD Palm (51) documented 7 % with STS, Jia (29) 1.3 %, and O'Hare (50) 17 %. As published by Petrovic Schuller (63), polidocanol foam caused fewer necroses than liquid polidocanol. The authors consider the amount of polidocanol in the extravasation as the cause, which is lower when foam is used rather than a fluid.

A burning sensation during the injection occurred in the air group 11.7 % of the time, in the CO_2-O_2 group 5.5 % , even though on average the the polidocanol concentrations and amounts were higher in the CO_2-O_2 group. Morrison (47) cites the numbers for experiencing a burning sensation with CO_2-O_2 foam at 7 %. Comparable among our air- and CO_2-O_2 group were post-injection pains, at 2.6 % and 2.5 % respectively. Morrison (47) cites an astonishing 22 % (air) and 20 % (CO_2-O_2), which means that the differences among the gas groups are comparable, if not the difference in total occurrence. One possible explanation might be the greater duration of therapy session with Morrison (47) and an increased tension in the patients that might have gone along with that (verbally communicated).

Matting after sclerotherapy is always an unpleasant side effect. MD Palm (51) documented an astonishingly high rate of 69 % in the sclerotherapy of varicose side branches with STS. Myers (48), in his compendium of the literature, reported a rate of less than 20 %. This side effect occurred in our air group in 1.4 % of the cases and in the CO_2-O_2 group not at all.

Thromboses were documented at 1.1 % in the air group (including one Pelvic Venous Thrombosis) and 1.6 % in the CO_2-O_2 group (two partial calf muscle vein thromboses, one of them in the contralateral, untreated leg), a rate encountered by other studies as well: with Jia (29) 1 %, Gillet (23) 0.6 % to 2 %, Regan (60) 7.4 %, Wright 70) 2.5 %. Particularly the result of Regan (60) prompted Gloviczki (25) to comment that further improvements of sclerotherapy techniques with foam were warranted. The results of both groups in our OS met this demand.

The literature points to the thrombosis rate rising relative to the amount of foam used. In our experience, consistent with Wright (70), treatment with low-molecular-weight heparin (LMWH) just for a few weeks and with sonographic check-ups, is sufficient to see the thrombosis recede entirely. All cases in the CO_2-O_2 group turned out completely reversible after 14 days of heparin therapy and the calf muscle vein thrombosis caused no post-thrombotic venous valve damage (▶Tab. 7).

Guex (26–28) showed that visual impairment occured in sclerotherapy with liquid polidocanol at 0.05 %, but in air foam sclerotherapy at 0.3 %, in other studies visual impairments occured in over 6–23 % (49, 50, 62, 71) a difference to which Sarvananthan (62) also points and which needs further attention.

The rarity in the air group does not correspond with reports in the international literature and may possibly be explained by the very small amount that was applied on average. Two of the cases of visual impairment occurred during the period before the dispenser was rinsed for 3 minutes each time before filling the syringes with the gases, which meant that residual nitrogen in the syringes had risen to up to 20 %. In more than 500 CO_2-O_2-sclerotherapy sessions that followed our OS in both centers, none reported further complications.

The numbers presented here combined with those in the publications of Beckitt (2), Morrison (47), Regan (60), and Wright (70) cover altogether 1160 treatments with CO_2-O_2 FS and about 1.5% treatment sessions led to cases of temporary visual impairment. This denotes a significant difference when compared to the data gathered from the literature about air-FS, which reveals 0,3–23% such cases (26–28, 49, 50). But even this lower rate of occurences of visual impairment is still higher than that after liquid sclerotherapy (26–28, 33). Liquid scle-

Tab. 7 Side effects polidocanol foam sclerotherapy (PFS) with CO_2-O_2 (in %).

	Wright (2006)	Morrison (2010)	Regan (2011)	Own results (2011)
Skin discoloration	49.7		37	13.6
Hematoma	9.2		6.1	2.5
Pain	34.3	22		2.5
Thrombosis	2.5	8.6	7.3	1.6
Visual defects	1.37	2	1.2	2.0

rotherapy is, however, significantly less effective (32, 55).

The cerebrovascular attack (CVA) is rarely but recurrently associated with air foam sclerotherapy (7, 18, 62). Therefore Bessereau published (3,4) his recommendation to the FDA (Food and Drug Administration) that the treatment of CVA required the availability of hyperbaric oxygen therapy. This recommendation is based on the iatrogenic air embolisms that occurred after treatment with several 100 ml of gas during laparoscopic surgery (30), where the complications did not differ whether CO_2 or air was used (22). For smaller quantities of iatrogenic air embolisms, the severity and frequency of CVAs caused by CO_2 was reduced (42, 67). This advantage should also be achieved by using CO_2-O_2-sclerotherapy.

Our OS observed no cases of CVAs in the form of TIA or stroke. Sarvananthan (62) documented 2011 in his thorough review that CVAs may occur even with small amounts of foam used in the FS, and that this side effect can also be observed during liquid sclerotherapy (15, 34, 38, 55), although less frequently. In all cases always existed an atrial septal defect (7, 31, 40). The review (62) doesn't mention, however, the air-block technique used in the liquid sclerotherapy – a common practice in France (57) that involves pre-injecting 0.3 to 0.5 ml air. The absence of CVA in this AWB is consistent with the work of Ceulen (11), Hamahata (32) and Yamaki (72), the groups used on average only 3.4 ml of foam. This is a contradiction to the meta-analysis of Sarvananthan (62) and other observations (14, 62).

Data on complications after FS involving TIA, impaired vision of varying duration, severe cough, tightness in the chest and vomiting can also be found in Jia (29), Gillet (23, 24), Guex (26–28) Morrison (45–47) and others (20, 33, 43, 50, 65). What is essential, as observed by Morrison (45, 47), is that a CO_2 (45) and better yet: a CO_2-O_2-FS (47) can reduce the above complications by more than half, and that all incidents following a CO_2-O_2-FS were completely reversible without additional therapy, which does not apply to air-FS. Neither amount of foam, foam concentration, release of endothelins, or cell debris can properly explain the cases of impaired vision and CVA (21, 24).

However, it has been shown that small bubbles from the foam can be found in the entire organism after FS (9, 23, 26, 40, 46, 61, 71). On CVA Bush (7) detected a local hypoechogenicity, Hahn (31) reported vascular closure. The possibility of vasospasm that has been postuated could not yet be verified in neurological and ophthalmological studies (23, 39, 54). Studies with very large numbers of patients are needed to document any significant differences, because these complications are rare. In a prospective study of Beckitt (2) on two times 253 legs with STS-air-foam vs. STS-CO_2-O_2 foam only one case of visual impairment was documented among the patients treated with air-foam.

Regarding all the side effects

Hyperpigmentation and hematomas decreased significantly under CO_2-O_2-FS. The lower number of phlebitis in the CO_2-O_2-FS is explained by the almost always done compression therapy and improved effectiveness. Burning, itching and pain were not siginificantly decreased by CO_2-O_2-FS compared to air-FS. The polidocanol-FS showed in our both groups significantly less matting compared to STS-FS. The same applies to the thrombosis rate. The rate of transient visual disturbances in the CO_2-O_2-FS corresponded to the literature, there were no CVA.

Many factors, not all of them yet fully studied, determine the effectiveness of FS, but the summary of CO_2-O_2-FS literature seems to offer advantages in effectivness and safety.

A roundup of the publications about the air-FS and CO_2-O_2-FS suggest the following:

- All studies of CO_2-O_2-FS used larger volumes of foam averaging 13.5 ml, whereas air-foam FS was conducted with an average of 6.1 ml.
- The CO_2-O_2-FS has fewer local side effects when it comes to hyperpigmentation and hematomas .
- The CO_2-O_2-sclerotherapy is more effective and takes fewer sessions CO_2-O_2, the different techniques of CO_2-O_2-foam preparation are negligible. The effectiveness increases with higher concentrations of polidocanol in the CO_2-O_2-FS.
- The physiological characteristics favor the use of CO_2-O_2 rather than air with 80 % N_2, since in well over 1000 applications of CO_2-O_2-FS no CVAs were recorded.

Finally it should be noted that during foam-sclerotherapy every effort should be made to avoid serious complications and further increase the safety of the already safe foam sclerotherapy (22).

Disclosure

The authors are co-inventors of the high-accuracy gas dispenser M2000DUO, to which Dr. G. Hesse holds the patents. Dr. Breu is an advisor to Kreussler Pharma Ltd.

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