

# Sclerosant foams

## Stabilities, physical properties and rheological behavior

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### Keywords

Sclerosant foam stability, Tessari, DSS, polidocanol, sodium tetradecyl sulfate

### Summary

Numerous ways of transferring detergent type liquid sclerosants into foam have been described. Out of all techniques, the three most commonly used around the world were selected. Sclerosant foams prepared with different agents and protocols were analyzed in detail, and their rheologic properties were assessed. Some of the results are presented in this review. **Results:** It is evident that the material for foam production plays an important role for foam stability, and – connected to this – maybe also for efficacy and safety. Therefore, material that ensures acceptable foam quality should be used exclusively. Out of a huge number of possibilities, the material described in this study was found most suitable. This ensures minimal reduction of foam quality delivered into the vein. Foams considered instable are not clinically ineffective. They have a greater efficacy than the corresponding liquid agent. Foams considered stable seem to need lower injection volumes to have the same or better physical behaviour. **Conclusion:** Since higher volumes of sclerosant foams are correlated with more side effects, always the smallest effective volumes of foams of appropriate quality are justified.

### Schlüsselwörter

Sklerosierungsschaum-Stabilität, Tessari, DSS, Polidocanol, Natriumtetradecylsulfat

### Zusammenfassung

Zahllose Möglichkeiten sind beschrieben, um aus flüssigen Detergenz-Sklerosierungsmitteln Schäume herzustellen. Die drei am häufigsten verwendeten der zahlreichen Techniken wurden gewählt. Sklerosierungsschäume, die mit unterschiedlichen Sklerosierungsmitteln und nach unterschiedlichen Herstellungsbeschreibungen generiert worden waren, wurden detailliert untersucht und ihre physikalischen Eigenschaften festgestellt. Einige der Ergebnisse werden beschrieben. **Ergebnisse:** Es ist eindeutig, dass das zur Schaumherstellung verwendete Material die Schaumstabilität erheblich beeinflusst, und – damit zusammenhängend – wohl auch Wirksamkeit und Sicherheit. Daher sollte ausschließlich Material verwendet werden, mit dem sich eine gute Schaumqualität sicher erreichen lässt. Aus einer Reihe ganz unterschiedlicher Möglichkeiten zeigte sich das hier beschriebene als das am Besten geeignete. Es sorgt dafür, dass die Qualität des intravenös gegebenen Schaums nur minimal sinkt. Instabile Schäume sind klinisch nicht ineffektiv, denn sie haben immer eine höhere Wirksamkeit als das zugrunde liegende flüssige Sklerosierungsmittel. Stabile Schäume aber benötigen offenbar geringere Injektionsvolumina um das gleiche oder ein besseres physikalisches Ergebnis zu erzeugen. **Schlussfolgerung:** Auch weil höhere Schaumvolumina mit mehr unerwünschten Nebenwirkungen korrelieren, sollte stets das geringste noch effektive Volumen eines Schaums ausreichender Qualität verwendet werden.

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**Sklerosierungsschaum: Stabilität, physikalische Eigenschaften und rheologisches Verhalten**  
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For the first time, a sclerosant had been used in the form of foam 60 years ago (54). Since only the detergent-type sclerosants offer the possibility of being foamed, no one really had reason to change from traditional injection of an ordinary liquid agent to foam injection before 1930, when sodium morrhuate, the first representative of detergent sclerosants, was introduced (53). It took almost another decade until McAusland started the development of a treatment method using foams for Sclerotherapy in 1939 (32). Since then, foam has been used especially after this new technique had been combined with concomitant duplex ultrasound imaging techniques in the nineties (29), the interest among phlebologists rose tremendously. Foam sclerotherapy has undergone a relevant evolution in the past decades (15, 16, 19, 33), particularly in the most recent one (53), but even today, research for a better understanding of this treatment is not finished (7, 8, 37, 38). Due to its effects, safety and economical advantages, foam sclerotherapy is frequently used for various indications, alone or in combination with other techniques (2, 20, 21, 24, 25, 28, 30, 43, 44).

Numerous ways of transferring detergent type liquid sclerosants into foam have been described (54), and some devices for intended future commercial use have been under development for more than 10 years (5, 6, 55). All these developments gave reason to Kreussler Pharma to start a project of therapeutical and technical improvements of its sclerosing agent Aethoxysklerol® containing polidocanol (POL) to search for a suitable technique for the preparation of a more standardized, but still economical “extemporary” sclerosant foam in the course of the 1990s at its premises in Wiesbaden. In parallel to this, a video was presented by Lorenzo Tessari in 1999, and his method, known as Tourbillon technique or Tessari method probably is the method of “extemporary” foam preparation used

most commonly around the world. A short time later, details of the method were published in print (45). Reasons for its widespread use presumably are that the method is easy, cheap, does not need special equipment (ordinary syringes, a 3-way tap, air or gases and some pumping movements are necessary) and allows quick production of a dense and creamy foam of quite a good quality (51, 52).

In the course of the project it was noted that sclerosant foams prepared with two syringe techniques allowed for some variation if minor changes were made during the preparation process, especially if changes were made in the material or in the way of performing and the number of the pumping movements (47, 50, 51). The variables affecting the properties of the foam in two-syringe-systems were changed systematically in an experimental series, with the aim to find out the optimal combination of

- sclerosant agent,
- sclerosant concentrations and
- manufacturing instructions.

The result is known as DSS\* (double syringe system) or “Tessari-DSS” which was presented at the UIP World Congress in Rome in 2001 (53). After 2001, experimental data concerning the influence of variables and their consequences on foam stability and properties were presented, and a number of practitioners started to integrate the technique in their daily clinical routine and in clinical trials (23, 26, 39). In 2005, an advanced ready-to-use version was presented by Kreussler Pharma, with enhanced blood

\* In a preliminary experimental series, different brands, types and sizes of syringes were tested, and in addition, various connectors. The combination of material that gave the highest foam stability (in terms of half-life and macroscopic appearance of the foam) was when 2 Injekt syringes, 10 ml, with luer lock (B. Braun Melsungen) were connected to a two-way-connector (female/female adapter, Combidyn, (B. Braun Melsungen)), when the amount of liquid sclerosant was 2 ml and the amount of air was 8 ml (ratio 1+4), and when the first pumping movements were made with an increased pressure. Unfortunately, using a syringe without a rubber plunger impedes a smooth and gentle injection, because the plunger gets stuck and moves uneasily during slow depression. Therefore, one Injekt syringe was replaced by one Omnifix syringe (with rubber plunger), which resulted in a good compromise between foam quality and injectability, i.e. the DSS-method (26, 52).

displacing capacities especially in veins of large calibers (48, 50) and tested in a prospective randomized multicenter clinical trial (40). The material is bundled in a kit and contains a special syringe precharged with sterile gas in the necessary amount tightly sealed by a particular two-way restrictor valve-adapter and allows easier production of a standardized foam, either manually or with the help of a special automated pumping device (27, 17).

## Material and methods

The experiments described were performed in the course of the mentioned research and development project. They highlight the influence of different input variables during foam preparation and compare the output properties of foams. Some experiments (1 to 3 and 5) have been performed to identify the best possible method of foam preparation with standard material and some compare properties of foams made with different methods and sclerosants.

All experimental work performed followed the “characterization of sclerosant foam” that was proposed by a subcommittee during the 1<sup>st</sup> European Consensus Meeting on Foam Sclerotherapy (1<sup>st</sup> ECMFS) (4). Mainly the input variables of foam production were part of the characterization, including

- type and concentration of the sclerosant,
- type of gas,
- relation of liquid and gas,
- method of preparation and
- time gap between processing and use.

The material was not explicitly part of the characterization at that time but as stated earlier, the author found that the choice of material clearly had a big influence on the outcome variables/foam properties.

The ECMFS characterization of sclerosant foam also included outcome variables, namely

- stability,
- viscosity, and
- bubble size.

The input parameters influence the outcome characteristics or properties of sclerosant foams. These foam characteristics

account for the action of foam i. e. mainly enhancement of efficacy, if compared to the action and effects of liquid sclerosants (4, 14, 26). For all experiments the following material was used.

## Foam production material

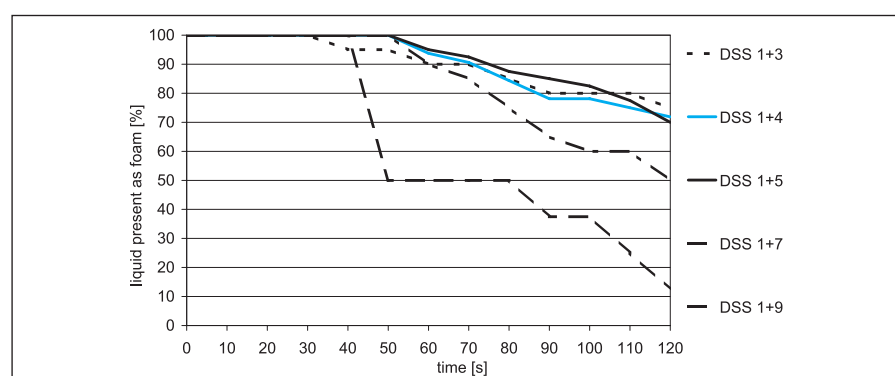
- Tessari method\*\* (T) (45): two Omnifix<sup>®</sup> syringes, 10 ml, Luer Lock (B. Braun Melsungen, Germany); 3-Way Stopcock, Discofix<sup>®</sup> C (B. Braun Melsungen, Germany).
- DSS technique (Tessari/DSS method) (DSS) (52, 26): one Injekt<sup>®</sup> syringe, 10 ml, Luer Lock (B. Braun Melsungen, Germany); one Omnifix<sup>®</sup> syringe, 10 ml, Luer Lock; one Combidyn<sup>®</sup> adapter w/w (two-way connector, B. Braun Melsungen, Germany).
- Polidocanol (POL): Aethoxysklerol<sup>®</sup> 0.5%, 1%, 2%, 3%: Chemische Fabrik Kreussler & Co. GmbH (Kreussler Pharma), Germany.

## Foam production methods

For the Tessari method, 8 ml of air were drawn up into the Omnifix syringe and 2 ml of sclerosant into the other syringe. Both syringes were connected to the 3-way stopcock which was turned into a 90°-position that allowed unrestricted flow between both syringes. The foam was made by alternately moving the plungers of both syringes completely forward and backward 5 times. Then the 3-way stopcock was rotated into an oblique position that still allowed communication between both syringes, but where the passage through the stopcock was narrower than before. Another 5 complete forward and backward movements were performed.

For the DSS/Tessari method, 8 ml of air and 2 ml of sclerosant were drawn up into the Omnifix syringe. The female/female-adapter was connected to the filled syringe, then to the empty Injekt syringe. Foam was prepared by rapidly and completely pressing down the plunger of the filled Omnifix syringe 5 times with a short, firm thumb

\*\* The material used by Tessari was not mentioned in the publication (45).



**Fig. 1** Foam stability at different ratios of liquid to air: At 120 seconds, foam degradation seems similarly low for foams prepared with DSS at ratios of 1+3, 1+4, and 1+5. At this time, 70–75% of the liquid sclerosant used is still present as foam, the remainder has already reverted to liquid. Dry foams (1+7 and 1+9) are less stable. Foam at the ratio 1+9 has almost completely disappeared after 2 minutes (90% of the liquid has drained from the foam). The test suggests that the optimal ratio lies between 1+3 and 1+5.

pressure of one hand. The thumb of the other hand held the plunger of the 2<sup>nd</sup> syringe, so that pumping was done against resistance, i.e. at an increased pressure. Then 7 complete forward and backward movements were performed, pumping the foam alternately from one into the other syringe. The whole procedure took 7–9 seconds.

## Experiments and results

In all experiments, standard laboratory environmental conditions were maintained.

### Experiment 1: optimal ratio for liquid sclerosant and gas

With the material and method described for DSS different ratios of liquid sclerosant (POL 3%) to gas (air) were tested. Foam half time (FHT), i.e. the time until half of the liquid used to produce the foam had reverted to the liquid state was measured. It was assessed with the syringe containing a known volume of foam of a known ratio of liquid and gas set upright on its plunger, allowing the draining liquid to collect along the scale of the syringe for quantitative detection. In the experiment the amount of drained liquid was recorded as a function of time after the end of foam production in 3 to 5 runs for each ratio and the average for the relative values was calculated (► Fig. 1):

## Results

Foams prepared with the DSS using 3% POL solution have the highest stability in terms of FHT if the ratio of liquid agent to gas ranged from 1+3 to 1+5. For these ratios less than 30% of the liquid agent used to prepare the foam had reverted to liquid after 120 seconds.

### Experiment 2: Identifying the most suitable syringes

After having identified the “best” liquid-to-air ratios different syringe brands and sizes were tested. Foam was prepared in a 1+4 ratio with different concentrations of sclerosant. Foam stability, i.e. FHT, was recorded as a function of time during 120 seconds after the end of foam production in 3 to 5 runs for each concentration, brand and size and the average for the relative values was calculated.

## Results

In general, disposable plastic syringes seemed better for foam preparation if they were of the “2 parts” type, i.e. without the rubber part at the piston. Unfortunately, it is hard to manage a smooth injection with such a type of syringe since there is no or almost no lubricant in them which is responsible for gentle sliding during injection. A “3

parts”-syringe with rubber piston seemed not so good for foam production but better for a smooth injection. The syringe brands identified as most suitable are listed in the Material and Methods section. During the experiments it was noted that even different sizes of the same brand of syringes resulted in different foam stability. Chosen from standard injection syringes 20 ml syringes were best for foam production but too big to handle. 10 ml syringes were 2<sup>nd</sup> best for foam production and allowed normal handling, followed by 5 ml and 2 ml syringes (► Fig. 2).

The smaller the syringe and the lower the sclerosant concentration, the faster the foam reverts to liquid and gas and/or the sooner liquid drainage begins.

### Experiment 3: Identifying the most stable foam

During experiments 1 and 2 it was noted that although the FHT of foams prepared with 10 ml syringes and at ratios of liquid agent and gas of 1+3, 1+4 and 1+5 was high there were differences concerning the onset of drainage and concerning the macroscopic appearance of the foam itself: At some point, macroscopically visible bubbles or “holes” within the foam appeared and it seemed that the time until this happened was different for different materials and different preparation methods. In experiment 3, experiment 1 (DSS, POL 3%, different ratios) was repeated but monitoring time was increased until the FHTs were reached and special attention was paid to the foam drainage time (FDT), i.e. the time until visible drainage within the foam began, measured with the syringe containing a known volume of foam of a known ratio set in an oblique position of 30–45°, allowing even tiny amounts of draining liquid to be detected qualitatively and foam coalescence/coarsening time (FCT), i.e. the time until visible bubbles (>250–300 µm diameter – thus just visible to the naked eye) appeared within the foam or bubble-free areas (indicating breakdown) appeared at the top of the syringe set upright on its plunger. The same was repeated for T foams. The FHTs, FDTs and FCTs were recorded as a function of time

after the end of foam production in 3 to 5 runs for each measurement and the average of the absolute values were calculated.

## Results

Foam half times were not the same for the 1+3, 1+4 and 1+5 foams, as would have been expected by the results of Experiment 1 (approximately same stability at 120 seconds). The longest FHTs were found for “wet” 1+2 and 1+3 foams. FDT were longest if the foams were “dry” (ratio of 1+4 and greater), but shorter in “wet” foams (1+1, 1+2, 1+3) (► Fig. 3). These foams started to revert into liquid sclerosant and gas almost immediately after foam production had been finished. Inversely, FCT was longest in wet foams and shortest in dry foams. Thus, the “most stable” foam is not identical to the foam with the longest FHT. Drainage and coalescence/coarsening have to be considered too. The most stable foams were foams of a ratio of 1+4 up to 1+5 (acceptable FHT, no visible drainage or coalescence/coarsening until ~ 35 to 55 seconds). With syringes smaller than 10 ml drainage was faster and/or coalescence/coarsening appeared earlier (► Fig. 3).

A comparison of the results of FHT and FCT between DSS and T foams is given in ► Table 1. T foams at a ratio of 1+1 had a longer FHT than DSS foams at the same ratio. For all other ratios FHTs were longer in DSS foams. FCTs were longer in any DSS foam ratio tested as compared to T foams at the same ratio.

## Experiment 4: Sclerosant concentration and foam stability

The DSS-technique (ratio 1+4) was tested with different POL concentrations. The relative amount of drained liquid sclerosant was recorded as a function of time after the end of foam production in 3 to 5 runs for each concentration and the average of the relative values was calculated (► Fig. 4).

## Results

Foam deterioration was quickest in foams made with low sclerosant concentrations: for 0.25%, 1% and 3%, the Foam Half-

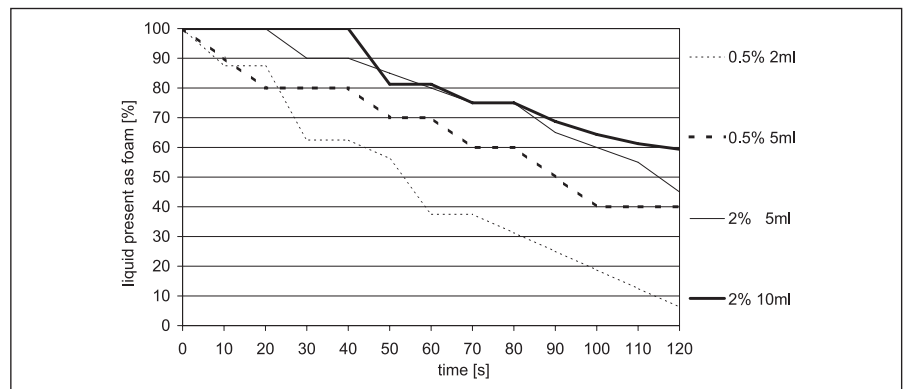


Fig. 2 Foam stability according to syringe size and concentration

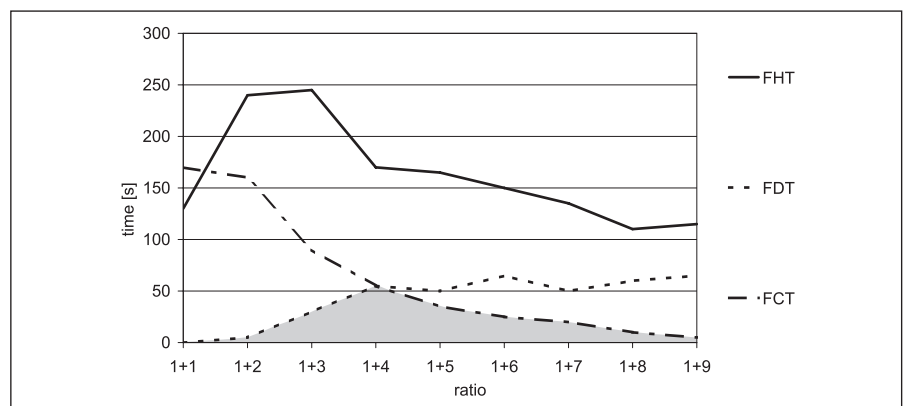


Fig. 3 Foam stabilities for DSS POL 3% at different ratios of liquid + air: The stability of foam cannot be stated looking at the foam half time (FHT) only. If so, foams of the ratio 1+2 or 1+3 were to be considered the most stable ones (long FHTs). But these foams start to revert to liquid and gas very soon after production, i.e. have a short foam drainage time (FDT) but do not show development of large bubbles for a long time, i.e. have a long foam coalescence/ coarsening time (FCT). Foams can be considered “stable” only below all curves (i.e. within the grey area under the curves). Maximum stability was found for 1+4 to 1+5 foams made with DSS and POL 3% (55 seconds)

Times (FHT) were 30, 130, and 180 seconds respectively (► Fig. 5). In low-concentration foams drainage began immediately after foam production was finished and large visible bubbles appeared within the foam very quickly. It was not possible to obtain homogeneous stable foam for more than a few seconds if POL 0.25% was used for foam preparation. Foam prepared with POL 3% was most stable in terms of FHT.

## Experiment 5: Influence of preparation on foam stability

To study the influence of different numbers and “speeds” of pumping movements on foam quality lots of different preparation protocols were carried out to finally define

the DSS. Especially the influences of different numbers of the “short” movements were tested (i. e. the movements where additional pressure has to be built up during the procedure – performed by rapidly pressing down the plunger of one syringe while the thumb of the other hand holds the plunger of the second syringe so that pumping must be done against this resistance). With some practice, a pressure of 6 to 8 bars can be built up, i.e. that the entire content of one syringe (10 ml = 8 ml of air and 2 ml of liquid agent) is compressed to only 3 or 3.5 ml content in the other syringe (1 to 1.5 ml compressed air and 2 ml of incompressible liquid agent). “Long” movements were just the back and forth pumping without additional pressure.

**Tab. 1** Stability of DSS and T foams at different concentrations of POL and ratios of liquid and air: The stability of T and DSS foams in terms of foam half time (FHT) and foam coalescence/ coarsening time (FCT). Wet foams have longer FHTs and FCTs than dry foams (foam drainage time not shown). Wet T foams have longer or similar FHTs than the corresponding DSS foams. FCT is longer in any DSS foam compared to the corresponding T foam.

liquid + gas	FHT (s)				FCT (s)			
	POL 1%		POL 3%		POL 1%		POL 3%	
	T	DSS	T	DSS	T	DSS	T	DSS
1 + 1	135	110	150	130	85	165	110	170
1 + 2	167	205	230	240	40	75	78	160
1 + 3	127	170	167	245	0	55	6	90
1 + 4	135	145	142	170	0	50	2	55
1 + 5	120	145	132	165	0	35	0	35
1 + 6	110	135	122	150	0	0	0	25

## Results

Foam preparation within 9 seconds gave acceptable foam, slower preparation resulted in less stable foam. If more “short” and/or “long” pumping movements were done the foam quality did not improve noticeably. If less “short” movements were done the foam quality decreased. The most stable foam resulted if 5 complete “short” pumping movements with pressure, followed by 7 complete “long” pumping movements, were performed within 7 to 9 seconds. It was not possible for the author to perform these manual movements in less than 7 seconds.

### Experiment 6: Influence of gases on foam stability

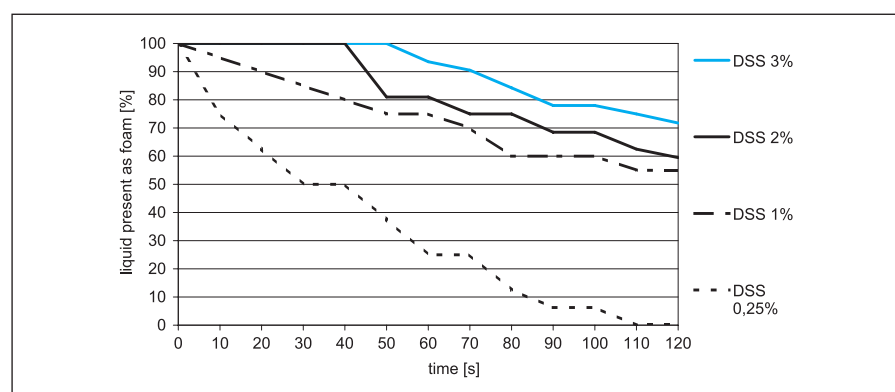
After having found the best possible ratio, sclerosant concentration, material and preparation protocol for air-based foams in the previous experiments, foam stability was tested with pure CO<sub>2</sub> instead of air. Intravenous CO<sub>2</sub> is known to be relatively safe (11), and some use mixtures of CO<sub>2</sub> and O<sub>2</sub>(8), which were not tested in this study. Foam was prepared with POL 3% according to the DSS protocol and the relative amount of drained liquid was recorded as a function of time during 120 seconds after the end of foam production in 3 to 5 runs for each concentration and the average was calculated (► Fig. 5).

## Results

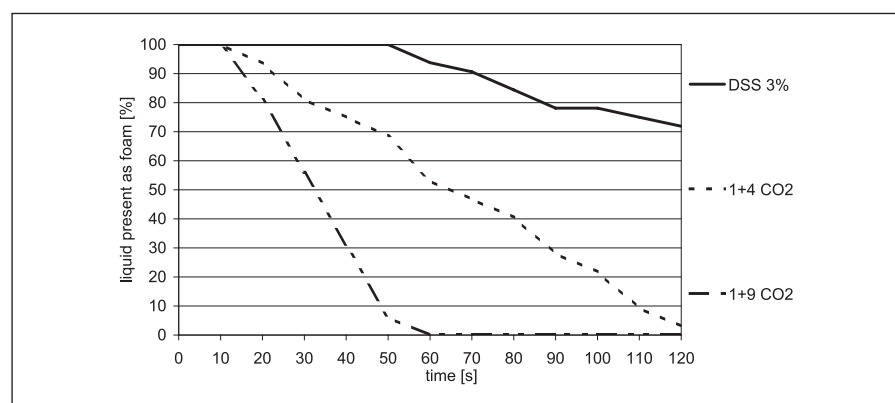
Foam stability was highest for DSS with air (ratio 1+4) (Foam Half-Time: 180 seconds) (► Fig. 6). At the same ratio, use of CO<sub>2</sub> as the gas component resulted in a much faster deterioration and appearance of large visible bubbles within the foam (FHT: 60 seconds). If the foam was made “drier” and the gas volume was increased to 1+9, foam stability was worse (FHT: 35 seconds).

### Experiment 7: Displacement effects of defined volumes of foams

Whereas experiments 1 to 6 were tests for foam stability under different protocols, ra-



**Fig. 4** Foam stability for DSS foam at 1+4 and different POL concentrations: The stability of DSS foam was highest if foams were prepared with high concentrations of sclerosant. As soon as 30 seconds after foam production half of the liquid used to prepare foam of 0.25% POL had reverted to its liquid state.



**Fig. 5** Foam stability of air-based and CO<sub>2</sub>-based DSS POL 3% foams: The stability of foam was highest if DSS foams were prepared with air at a ratio of 1+4 and POL 3%. Replacement of air with CO<sub>2</sub> in the same ratio resulted in faster deterioration. FHT for air-based DSS foam (1+4, POL 3%) was 180 seconds, whereas it was 60 seconds for CO<sub>2</sub>-based DSS foam (1+4, POL 3%) and 35 seconds for CO<sub>2</sub>-based DSS foam (1+9, POL 3%).

tios, materials, sclerosants and concentrations, experiment 9 was done to characterize foam viscosity, one of the outcome variables suggested by the 1<sup>st</sup> ECMFS (4). In clinical use, injection of viscous foams is done to displace blood out of the treated vein segment to allow prolonged direct contact between sclerosant and endothelium without immediate dilution (14, 31). In this experimental setting, foam viscosity was not measured with a rheometer device directly but its ability/capacity to displace liquid (water) out of a segment of a plastic tube which was placed in an oblique position to be close to the “elevated leg” position (► Fig. 6). If foam behaved like a liquid it would rapidly be floating away or only float below the upper wall of the tube. However, sclerosant foams can behave like an elastic solid and form a short lasting “plug” that temporarily completely displaces the water in the tube. To form such a plug the foam must be viscous enough so that it can resist the forces exerted by the water in the tube (► Fig. 6).

The injected volume of foam was related to the tube diameter chosen so that its volume would have been enough to fill a cylinder of a length that is 20 times its diameter (► Fig. 7, segment 1). Different foams (concentrations, ratios, methods) were injected using a 21G injection needle. After injection of the foam the maximum extension of the foam plug (length of the tube segment completely filled with foam) was measured on the lower wall of the tube and given as a factor (n) in terms of the n-fold of the tube diameter as the maximum displacement distance ( $MDD_{(n)}$ ). In addition, the time was recorded until the foam plug had no more contact to the lower circumference, i.e. when bubbles were just floating below the upper wall of the tube segment (maximum displacement time (MDT)). After each injection, all contents were removed from the tube and the tube was cleaned and filled with fresh water. All injections and measurements were repeated at least three times and the average values were calculated (► Fig. 7).

## Results

In no case of foam injection could the foam fill the complete segment which would have been possible in theory (► Fig. 8, seg-

ment 1). After injection of some foams no plug developed at all and the foam bubbles were rapidly moving only along the upper wall of the tube towards its open end ( $e'$ ) (► Fig. 8, segment 3). This was also true if foam injections were done slowly: bubbles were immediately floating from the opening of the needle to the upper wall of the tube. Only if injections were done quite rapidly a foam plug with an appearance similar to segment 2 in ► Figure 8 sometimes developed. Depending on the type of foam up to a ratio of 1 + 5 and on the tube diameter, the  $MDD_{(n)}$  typically did not exceed 8 or 9, i.e. only 40–45% of the theoretically possible value of 20.

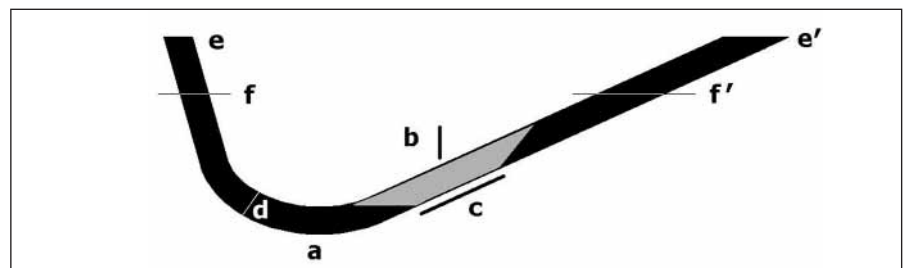
Very wet foams (ratio 1+1) did not form a foam plug in tubes of 5, 7 or 9 mm diameter. A small plug was only visible in the 4 mm tube. Foams of a dryer ratio (1+2) had much better displacement capacities in 4 and 5 mm tubes but did not show any plug in the 9 mm tube. The best displacement effects (highest  $MDDs$ ) were reached in any

tube if the ratio was 1+4 or 1+5. Foams dryer than 1+5 did not change the  $MDDs$  significantly. The bigger the tube diameters were, the harder it was to obtain a foam plug. Inversely, in tubes of smaller diameter even very wet (liquid-like) foams caused (at least some) displacement.

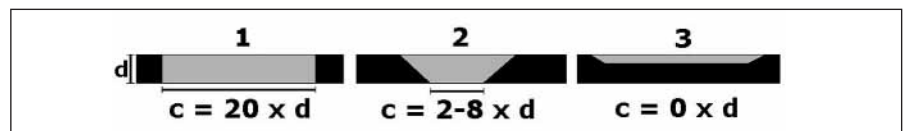
If a foam plug developed after injection the time was recorded until the foam plug had no more contact to the lower circumference. This MDT in general was short for wet foams and longer for dry foams and was longer in tubes of small and shorter in large diameter tubes (► Fig. 9).

Interestingly, 1+4 or 1+5 foams which had the highest  $MDDs$  in all tested tubes remained as a “plug” for about 12 to 20 seconds in large diameter tubes but remained more than double (!) the time if the diameter was small (up to 40 seconds).

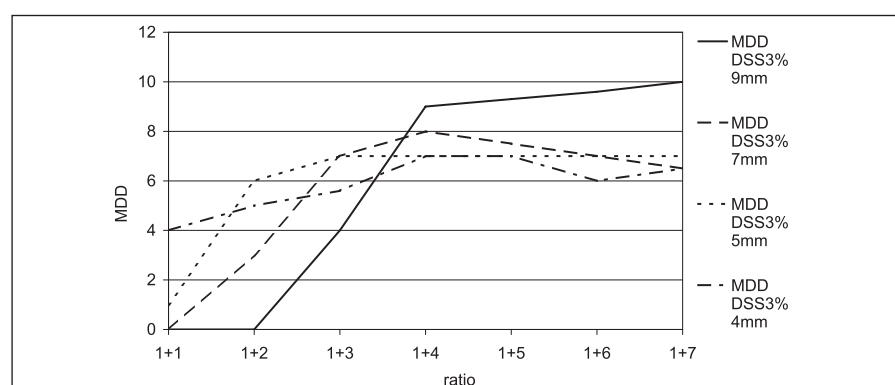
A comparison of  $MDDs$  and  $MDTs$  between DSS and T foams at 1% and 3% is given in table 2.  $MDD$  and  $MDT$  were highest in 1+4 and 1+5 DSS foams. Noticeably,



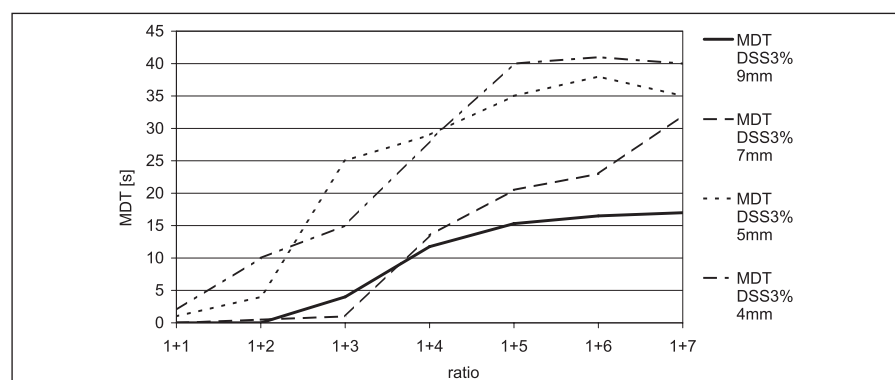
**Fig. 6** Experiment 7: A plastic tube (length approx. 100 cm, inner diameter (d) 4, 5, 7 or 9mm) was placed between lab pods so that both open ends of the tube ( $e, e'$ ) were placed at the top and one point of the tube was placed at the lowest point (a). From this a long straight part of the tube was ascending at an angle of about 25° (segment a-e'), and the shorter part of the tube was ascending at an angle of about 80° (segment a-e). Water was filled into the tube until it reached level (f) and (f'), about 20 cm above the lowest point (a). Close to point (a) sclerosant foam was injected into the slightly ascending part of the tube (b), allowing foam bubbles to float towards ( $e'$ ). The maximum length of the foam plug (complete filling of the tube) was measured at the lower wall of the tube (c).



**Fig. 7** Appearances of foams in a tube segment: Segment 1 shows ideal filling of the tube with a foam volume chosen so that it would have been enough to fill a cylinder whose length (c) is 20 times the diameter (d). Segment 2 shows one possible “real filling” of the tube, where the length of the foam plug (c) (length of foam contact to the lower wall) was typically between 2 and 8 times the diameter (d), i.e. a maximum displacement distance (MDD) of 2–8. Some foams did not form a plug after injection at all (foam did not have contact to the lower wall of the tube), another possible appearance of “real filling” ( $MDD_{(n)}: 0$ ).



**Fig. 8** Displacement capacity of DSS foam with POL 3% at different ratios and tube diameters: maximum displacement distance (MDD) for DSS POL 3% in different tube diameters is highest if foams at a ratio of 1+4 or 1+5 are injected ( $MDD_{(n)}$ : 7–9). In tubes with smaller diameters wet foams have some displacement effect ( $MDD_{(n)}$ : 4) but not in large diameter tubes ( $MDD_{(n)}$ : 0). A 1+2 foam has no effect in a 9 mm tube ( $MDD_{(n)}$ : 0) but shows almost maximum displacement in a 4 mm tube ( $MDD_{(n)}$ : 6).



**Fig. 9** Displacement times of DSS foam with POL 3% at different ratios and tube diameters: Wet foams (1+1 and 1+2) only (if at all) form a short lasting plug, especially in large diameter tubes. Dry foams (1+4 and 1+5) have a good displacing effect for a relatively long time in big diameter tubes but stay very long in small diameter tubes.

**Tab. 2** Displacement distances and times for DSS or T foams with POL 1% or 3% at different ratios: Maximum displacement distances (MDD) and Maximum displacement times (MDT) of DSS or T foams with POL 1% or 3% in a 7mm tube at different ratios. MDDs are factors (n-fold of the tube diameter) indicating the maximum extension of a foam plug after injection of a defined foam volume. An  $MDD_{(n)}$ : 0 means that no foam plug was seen. MDTs are given in seconds and indicate how long it took until a foam plug had dissolved after injection. An MDT of 1 means that a foam plug was seen, but dissolved immediately after the injection stopped.

liquid + gas	MDD <sub>(n)</sub>				MDT (s)			
	POL 1%		POL 3%		POL 1%		POL 3%	
	T	DSS	T	DSS	T	DSS	T	DSS
1 + 1	0	0	1	0	0	0	1	0
1 + 2	1	1	3	3	0	0.5	1	2
1 + 3	1	3	4.3	7	1	1	4	9
1 + 4	1	7	5	8	1	13.5	9.5	24.5
1 + 5	1	6.7	6	7.5	1	20.5	13	28.5
1 + 6	1	7.5	6.5	7	1	23	19.	23.5

at these ratios the MDD values did not differ much (although it took longer until a DSS POL 3% foam plug had gone) (► Tab. 2).

### Experiment 8: Minimum foam volumes causing displacement

Contrary to experiment 7 (where a predefined volume of sclerosant foam was injected into tubes and the outcome was measured), experiment 8 was done to find out the minimum required foam volume that was just about able to form a foam plug after injection, i.e. to show minimal displacement - minimum displacement volume (MDV). The setting was identical to the one described before only that injection volumes started at  $n = 1$  (each injection volume was calculated to theoretically fill a tube segment of a length which was the n-fold of its diameter) and were constantly increased in steps of 1 ( $n = 2, n = 3$  etc.) until a complete (even if short and/or short-lasting) displacement was noted. Experiment 10 was done in tube diameters of 5, 7, and 9 mm with DSS POL 3% foams at ratios between 1+1 and 1+6. After each injection all contents were removed from the tube and the tube was cleaned and filled with fresh water. All injections and measurements were repeated at least three times and the average values were calculated.

### Results

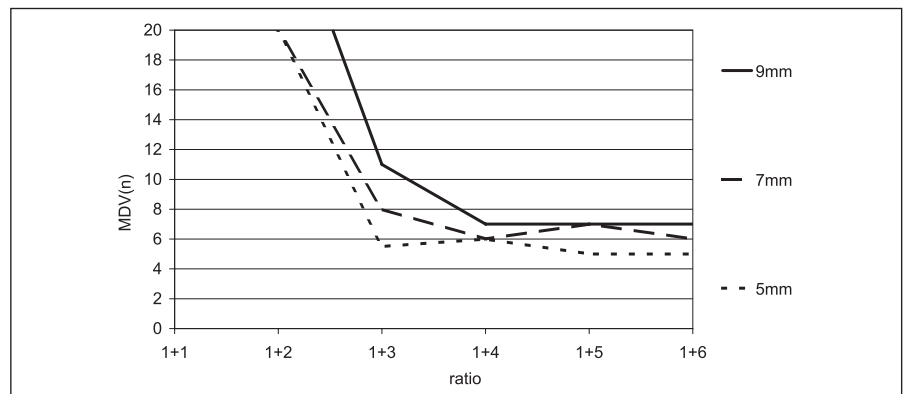
If wet foams (1+1 or 1+2) were injected, the minimum displacement volume (MDV) to obtain a foam plug had to be large enough to fill a cylinder of a length of 20 to more than 30 times the tube diameter ( $MDV_{(n)} 20 \rightarrow 30$ ) (► Fig. 10). With 1+3 foams the required volumes were lower, depending strongly on the tube diameter ( $MDV_{(n)} 6-11$ ). With 1+4 foam the required volumes were lowest, (almost) *irrespective* of the tube diameter and had values of  $n = 5-7$ . With dryer foams the MDV did not increase any more (► Fig. 10).

Calculated back to “real” foam volumes, 50% less volume was required if a 1+4 foam was injected instead of a 1+3 foam in 9 mm tubes and 30% less in 7 mm tubes. In 5 mm tubes the MDVs for 1+3 and 1+4 foams were the same (► Tab. 3).

## Discussion

Foam sclerotherapy critically relies on the properties of foamed sclerosant solutions, i.e. the outcome variables, namely stability, viscosity, and bubble sizes (4, 14, 31). In clinical use, the time between the end of foam preparation and its clinical application (i. e. injection) should be shorter than the time until relevant foam destruction begins. Therefore, the choice of foam production techniques and material that ensure high foam stability should be preferred. Highest foam stability in the syringes resulted if the DSS technique was used, especially with higher concentrations of sclerosants, and very similar results can be reached using the EasyFoam kit\*\*\* (EF). Rao and Goldman have published data about foam half lives with POL and STS at low concentrations (42). They obtained similar – but not identical – data, compared to results presented earlier (49, 52, 51) and/or in this study. It is not astonishing that the foam half times measured by Rao were shorter than the FHTs found here, because the material used and the methodology of foam production in the study by Rao were not identical to the material and methods described before (26, 51, 54, 44) and used in the present report: Rao and co-workers used smaller syringes (5 ml and 3 ml, i.e. with higher relative silicone content) of a different brand, the pumping movements were done less often, in the case of the Tessari method (with 3-way tap) without rotation of the stopcock to a narrower position and in the case of DSS technique without any additional pressure. All changes reduced foam stability, as compared to results described herein. In accordance with own results Rao found longer foam half-times if

\*\*\* EasyFoam® Kit for standardized foam production (1 syringe 5 ml, Luer lock; 1 syringe 10 ml, female outlet, Luer lock, precharged with sterile gas (air) and sealed with bidirectional restrictor valve adapter for automatic opening on connection/closure on disconnection of the 5 ml syringe); Laboratoire Kreussler Pharma, France. For foam production with EasyFoam, 1.6 ml of sclerosant is drawn up into the 5 ml syringe. This syringe is connected to the bidirectional restrictor valve of the 10 ml syringe. The whole content of both syringes is pumped 10 times completely back and forth without interruptions and within 9–11 seconds from one syringe into the other and back.



**Fig. 10** Minimum displacement volumes for DSS foam with POL 3% at different ratios in different tube diameters: Wet foams (1+1 and 1+2) require large volumes to form a foam plug (MDV(n): > 30). 1+3 foams require a smaller volume (MDV(n): 6–11) and dry foams (1+4 and 1+5) require the smallest volumes (MDV(n): 5–7).

higher concentrations of POL were used, lower foam half-times if STS was used and no significant difference in foam half-times for various concentrations of STS.

As shown in this study, for the evaluation of the stability of foam, assessment of its half-time (i.e. drainage) only is not sufficient since foam destruction is not only its separation into its initial phases (liquid and gas) but also becomes apparent with regards to the time of onset of drainage and the occurrence of visible (i.e. large) bubbles within the foam. In figure 2 of Rao's publication multiple macroscopic bubbles are visible everywhere within the foam-filled syringe (42). Such "holes" in the foams have been qualitatively assessed in the present study and they help to distinguish between different foam qualities. Looking at this parameter, foams prepared with the DSS-technique at a ratio of 1+4 or 1+5 showed highest stability.

The bubble size in general is a key parameter that determines also other foam properties:

- The contact surface of the foam that interacts with the target structures within the vein (i.e. endothelial cells): the smaller the bubbles the higher this contact surface (14). An increased efficacy should result from smaller bubbles.
- Bubble size influences the time it takes for a bubble to dissolve in liquid (13): Large bubbles need longer to get dissolved or absorbed, so an increased safety can be expected from smaller bubbles.

Right after generation the bubbles in all sclerosant foams tested are small, (depending on the boarders set) more or less mono-disperse or homogenous. Due to aging foam bubbles get larger and its bubble size distribution changes from more or less

**Tab. 3**

Minimum displacement volumes for DSS POL 3% at two ratios in different tube diameters: Real foam volumes (in ml) and minimum displacement volumes (MDV) for DSS foam with POL 3% (1+3 or 1+4). Values in blue cells were measured, values in grey cells were calculated. (n) indicates the factor by which the diameter is multiplied to get the length of the cylinder segment.

tube diameter (mm)	DSS POL 3%		
	ratio 1 + 3		ratio 1 + 4
	MDV <sub>(n)</sub> 6–11	MDV <sub>(n)</sub> = 6	MDV <sub>(n)</sub> = 7
10		4.7	5,5
9	6.3 <sub>MDV(n)=11</sub>	3.4	4.0
8		2.4	2.8
7	2.2 <sub>MDV(n)=8</sub>	1.6	1.9
6		1.0	1.2
5	0.6 <sub>MDV(n)=6</sub>	0.6	0.7
4		0.3	0.4

mono- to more or less polydisperse or inhomogeneous, mainly due to drainage and coarsening\*\*\*\*. If circulating in blood, relatively small air bubbles are reabsorbed in about 90 seconds, and smaller bubbles are reabsorbed even faster (12). In aged foams more and more bubbles become visible as the foam degrades. Large bubbles do not only decrease contact surface in the vein, and are not only dissolved more slowly but also have an influence on the rheological behaviour of the foam, i. e. they cause decreasing yield stresses, hence an inferior capacity to displace water out of tubes and maybe also the blood out of the vein.

In this study it was shown that foams have or have not the capacity of displacing liquid out of tubes. Of course water has another viscosity than blood, plastic tubes are different from veins, so that the results cannot be transferred into clinical recommendations directly. In the first randomized clinical trial comparing foam and liquid sclerosant, Hamel-Desnos et al. injected 2 to 2.5 ml of sclerosant foam into great saphenous veins of 4 to 8 mm diameter (26). Occlusion after one year was successfully reached in 84% of the patients, and the average length of occlusion was 28 cm. In an 8 mm vein, 2.5 ml of foam correspond to an "ideally filled" vein segment of approximately 5 cm length before vasospasm occurs and (having reduced its diameter by 50%) to 20 cm after spasm occurs. If the vein diameter is 7 mm the lengths before and after spasm occurs are 6.5 and 26 cm respectively, thus very close to the 28 cm occlusion length reported in the study (26). The minimum foam volumes that were just about able to cause displacement (of water in a tube) found for a 1+4 or 1+5 DSS foam in this study need to correspond to a cylinder whose length measures 6 to 7 times its diameter. In case of DSS foam this means 2.4 to 2.8 ml of foam for an 8 mm tube, which is very close to the foam volume in-

jected in the trial by Hamel-Desnos (2.5 ml) into that 8 mm veins.

Clinical studies show that the efficacy of DSS foams at a ratio of 1+4 prepared with POL 1% or 3% is very similar (9, 27). This can be explained with similar stability and rheology of both foams, as found in this study (foam half times, foam coalescence/coarsening times and maximum displacement distances).

The data presented also show that most foams have very good displacement effects and stay very long in tubes of small diameters. Clinically, a greater efficacy for foams in small vessels has been shown but also more local side effects (1). Maybe the foam just stays too long in small vessels, as suggested by the results of this study. Published data also show more systemic side effects if foam is given into small vessels (22). There are two possible explanations for this, supported by the findings of this study:

- The displacement effects of foams increase as the tube diameter gets smaller: In reticular veins and telangiectasia it can be expected that foam displaces even better and stays even longer than what has been shown in 4 mm tubes. Staying longer in the vein gives more time for foam aging, thus larger bubbles would develop within the veins. Larger bubbles and the absence of blood which otherwise would reabsorb gas bubbles within short, helps that bubbles grow. Transient mild neurologic events have been reported to occur more frequent after injection of foams into small vessels (22). Maybe these larger bubbles which are absorbed more slowly contribute to these systemic effects.
- The other possible explanation is just a simple calculation based on the findings of this study: 1 ml of foam injected into an 8 mm vein would *ideally* fill a vein segment of 2 cm and thereby destroy about 5 cm<sup>2</sup> of endothelium (spasm not included). The same amount injected into a 1 mm vein would (almost) fill 127 cm of this vein and thereby destroy 40 cm<sup>2</sup> of endothelium. Maybe just an increased release of much more of vasoactive agents cause (in predisposed patients) some reaction, typically migraine with visual disturbances, which could be examined in future studies.

With the results of the study and correlated clinical findings injection of sclerosant foams – if justified by the vein size – is recommended if the foam

- has small bubbles,
- is monodisperse and homogenous, and
- is as freshly prepared as possible.

It is evident that the the material plays an important role for foam stability, and – connected to this – maybe also for efficacy and safety. Therefore, material that ensures acceptable foam quality should be used only. Out of a huge number of possibilities, the material described in this study was found most suitable. The author has recognized also foam deterioration if foam was pushed through additional devices such as catheters. If injections are done with butterfly needles or catheters it is recommended to rinse the devices before foam is pushed through. This ensures minimal reduction of foam quality delivered into the vein.

Of course, foams considered instable or only having poor displacing effects in this study are not clinically ineffective. They always have a greater efficacy than the corresponding liquid agent but the efficacy seems somehow lower and the volumes injected seem to be higher (35, 36). Higher volumes of sclerosant foams are correlated with more side effects, thus the smallest effective volumes (not exceeding recommended doses (3, 4, 10, 41) or volumes found safe in randomized, multi-centre (27, 35) or non-randomized, single-centre trials) (34) of foams of appropriate quality are justified.

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#### Conflict of interest

The author declares, that there is no conflict of interest.

\*\*\*\* Coarsening – one of the principal aging mechanisms that destabilize the foam structure – is due to a gas exchange between neighbouring bubbles where larger bubbles grow at the expense of smaller ones (46). If all bubbles have the same size, this kind of gas exchange is strongly slowed down (18). Therefore, polydisperse foams generally coarsen faster than monodisperse foams.

## References

- Benigni JP, Sadoun S. Télangiectasies et varices réticulaires – Traitement par la mousse d'Aetoxiscélrol à 0.25 % – Présentation d'une étude pilote – *Phlébologie* 1999; 52: 283–289.
- Bergan J, Cheng Van Le. Treatment of recurrent varicose veins by sclerosant foam. In: Bergan J, Cheng Van Le, editors. *Foam sclerotherapy: A textbook*. London: Royal Society of Medicine Press Ltd. 2008: 193–197.
- Breu FX, Guggenbichler S, Wollmann JC. 2<sup>nd</sup> European Consensus Meeting on Foam Sclerotherapy, April 28–30, 2006, Tegernsee, Germany. *VASA* 2008; 37 (Suppl 71): 3–29.
- Breu FX, Guggenbichler S. European Consensus Meeting on Foam Sclerotherapy. *Dermatol Surg* 2004; 30: 709–717.
- BTG plc Press Release: Interim Results, 05 November 2009. [www.btgplc.com/view.aspx?ID=204&year=2009](http://www.btgplc.com/view.aspx?ID=204&year=2009)
- BTG plc Press Release: Proposed 2 for 5 rights issue, 12 February 2004. [www.btgplc.com/view.aspx?ID=204&year=2004](http://www.btgplc.com/view.aspx?ID=204&year=2004)
- Cavezzi A, Tessari L, Cabrera Garrido AL. Biocompatible gases in foam Sclerotherapy. *Aust N Z J Phlebol* 2008; 11: 86–87.
- Cavezzi A, Tessari L, Rosso M, Cabrera Garrido A. Variables in foam sclerotherapy with tessari method: Experimental data. In: XVI World Congress of the Union Internationale de Phlébologie; 2009 Aug 31–Sept 04; Monaco. *Int Angiol* 2009; 28 (Suppl 1): 9.
- Ceulen RPM, Bullens-Goessens YIJM, Pi-Van De Venne SJA. Outcomes and side effects of duplex-guided sclerotherapy in the treatment of great saphenous veins with 1% versus 3% Polidocanol foam: Results of a randomized controlled trial with 1-year follow-up. *Dermatol Surg* 2007; 33: 276–281.
- Deutsche Gesellschaft für Phlébologie. Guidelines for diagnosis and therapy of venous ulcers (version 8/2008). *Phlébologie* 2008; 37: 308–329.
- Durant TM, Stauffer HM, Oppenheimer MJ, Paul RE. Safety of intravascular carbon dioxide and the use for roentgenologic visualization of intracardiac structures. *Ann Int Med* 1957; 47: 191–201.
- Eckmann DM, Kobayashi S. Microvascular embolization following Polidocanol microfoam sclerosant administration. *Dermatol Surg* 2005; 31: 636–643.
- Epstein PS, Plesset MS. On the stability of gas bubbles in liquid-gas solutions. *J Chem Phys* 1950; 18: 1505–1509.
- Flückiger P. Nicht-operative retrograde Varicenverödung mit Varsylschaum. *Schweiz Med Wochenschr* 1956; 48: 1368–1370.
- Frullini A. New technique in producing sclerosing foam in a disposable Syringe. *Dermatol Surg* 2000; 26: 705–706.
- Gachet G. Une nouvelle méthode simple et économique pour confectionner de la mousse pour sclérose échoguidée. *Phlébologie* 2001; 54: 63–65.
- Gallenkemper G. Foam sclerotherapy: long term foam reproduction of Polidocanol-foam. Two trials with different concentrations under standardized conditions. *Phlébologie* 2008; 37: 10–15.
- Gañán-Calvo AM, Fernández JM, Oliver AM, Marquez M. Coarsening of monodisperse wet microfoams. *Applied Physics Letters* 2004; 84: 4989–4991.
- Garcia Mingo J. Esclerosis venosa con espuma: „Foam medical system“. *Rev Espan Med Cirugia Cosmet* 1999; 7: 29–31.
- Geroulakos G, Davies AH. Crosssection and foam: Has it got a role in the contemporary management of primary varicose veins? *Phlebology* 2009; 24: 1–2.
- Gonzalez-Zeh R, Armisen R, Barahona S. Endovenous laser and echo-guided foam ablation in great saphenous vein reflux: one year follow-up results. *J Vasc Surg* 2008; 48: 940–946.
- Guex JJ, Allaert FA. Immediate and midterm complications of sclerotherapy: Report of a prospective multicenter registry of 12173 sclerotherapy sessions. *Dermatol Surg* 2005; 31: 123–128.
- Guggenbichler S, Breu FX. Survey on the use of foam sclerotherapy in 2005. 6<sup>th</sup> European American Congress on Venous Diseases, 26–28 May 2005, Prague, Czech Republic. *Praktická Flebologie* 2005; 14: 55.
- Hahn M, Schulz T, Jünger M. Outcome four years after transcatheter foam sclerotherapy of the greater saphenous vein. *Phlebologie* 2008; 37: 237–240.
- Hahn M, Schulz T, Jünger M. Sonographically guided, transcatheter foam sclerotherapy of the great saphenous vein. Medical and economic aspects. *Phlebologie* 2007; 36: 309–312.
- Hamel-Desnos C, Desnos P, Wollmann JC, Ouvry P, Mako S, Allaert FA. Evaluation of the efficacy of polidocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: Initial results. *Dermatol Surg* 2003; 29: 1170–1176.
- Hamel-Desnos C, Ouvry P, Desnos P, Allaert FA. Mousse de Polidocanol à 3% versus 1% dans la sclérotérapie de la grande veine saphéne: Essai contrôle randomisé en double aveugle avec un suivi de 2 ans. Étude 3/1. *Phlébologie* 2008; 61: 103–109.
- Kabnick LS, Cayne N, Jacobowitz G, Lamparello P, Maldonado T et al. Endovenous procedures in varicose veins. What is the best choice today? *Phlebologie* 2008; 37: 229–236.
- Knight RM, Vin F, Zygmunt JA. Ultrasonic guidance of injection into the superficial venous system. *Phlébologie* '89. Davy A, Stemmer R (eds). John Libbey Eurotext Ltd 1989; 339–341.
- Luebke T, Brunkwall J. Systematic review and meta-analysis of endovenous radiofrequency obliteration, endovenous laser therapy, and foam sclerotherapy for primary varicosis. *J Cardiovasc Surg (Torino)* 2008; 49: 213–233.
- Mayer H, Brücke H. Angiologie – Zur Ätiologie und Behandlung der Varizen der unteren Extremitäten. *Chir Prax* 1957; 4: 521–528.
- McAusland S. The modern treatment of varicose veins. *Med Press Circular* 1939; 201: 404–410.
- Monfreux A. Traitement sclérosant des troncs saphéniens et leurs collatérales de gros calibre par la méthode mus. *Phlébologie* 1997; 50: 351–353.
- Morrison N, Neuhardt DL, Rogers CR, McEown J, Morrison T, Johnson E, Salles-Cunha SX. Comparisons of side effects using air and carbon dioxide foam for endovenous chemical ablation. *J Vasc Surg* 2008; 47: 830–836.
- Myers KA, Jolley D, Clough A et al. Outcome of ultrasound-guided sclerotherapy for varicose veins: Medium-term results assessed by ultrasound surveillance. *Eur J Vasc Endovasc Surg* 2007; 33: 116–121.
- Myers KA, Jolley D. Factors affecting the risk of deep venous occlusion after ultrasound-guided sclerotherapy for varicose veins. *Eur J Vasc Endovasc Surg* 2008; 36: 602–605.
- Parsi K, Exner T. Technique alterations including leg elevation, immobility, using filters or CO<sub>2</sub> gas do not prevent bubbles from reaching the right heart during foam Sclerotherapy. 11<sup>th</sup> Annual Scientific Meeting of Australasian College of Phlebology; 2007 Sep 18–22; Double Bay, Australia; *Aust N Z J Phlebol* 2008; 11: 85–86.
- Parsi K. Catheter-directed Sclerotherapy. *Phlebology* 2009; 24: 98–107.
- Partsch B. Möglichkeiten der Schaumsklerotherapie. *Zeitschrift für Gefäßmedizin* 2009; 6: 12–15.
- Rabe E, Otto J, Schliephake D, Pannier F. Efficacy and safety of great saphenous vein sclerotherapy using standardised polidocanol foam (ESAF): A randomised controlled multicentre clinical trial. *Eur J Vasc Endovasc Surg* 2008; 35: 238–245.
- Rabe E, Pannier F, Gerlach H, Breu FX, Guggenbichler S, Wollmann JC. Leitlinien: Sklerosierungsbehandlung der Varikose. *Phlebologie* 2008; 37: 27–34.
- Rao J, Goldman MP. Stability of foam in sclerotherapy: difference between sodium tetradecyl sulfate and polidocanol and the type of connector used in the double syringe system (DSS) technique. *Dermatol Surg* 2005; 31: 19–22.
- Reich-Schupke S, Altmeyer P, Stücker M. Therapy of insufficiency of the great saphenous vein with catheter-assisted micro-foam therapy without heparin. *Phlebologie* 2008; 37: 198–203.
- Stücker M, Kobus S, Altmeyer P, Reich-Schupke S. Sclerotherapy with foamed sclerosants. In: Rabe E, Wollmann JC (eds). *Sclero Guide*. Bonn: Rabe Medical Publishing 2009: 65–75.
- Tessari L. Nouvelle technique d'obtention de la scléro-mousse. *Phlébologie* 2000; 53: 129.
- Weaire D, Phelan R. The physics of foam. *J Phys: Condens Matter* 1996; 8: 9519–9524.
- Wollmann JC. An experimental model to pinpoint properties and behavior of sclerosing foams. *American College of Phlebology 17<sup>th</sup> Annual Congress*, San Diego, California, August 27–31, 2003.
- Wollmann JC. Device for producing a medical foam. *European Patent Office*, EP1796761A1; 27.09.2005.
- Wollmann JC. Herstellung und Eigenschaften von Sklerosierungsschaum. *Vasomed* 2004; 16: 24.
- Wollmann JC. Is there a need to standardize the preparation and the use of sclerosing foam? *Int Angiol* 2005; 24: 122.
- Wollmann JC. Properties and behaviour of sclerosing foams. 6. *International Phlebological Symposium*, 7–9 November 2003, Bologna, Italy.
- Wollmann JC. Schaum – zwischen Vergangenheit und Zukunft. *Vasomed* 2002; 16: 34–35.
- Wollmann JC. The history of sclerosant foam: persons, techniques, patents and medical improvements. In: Bergan J, Cheng Van Le (eds). *Foam sclerotherapy: A textbook*. London: Royal Society of Medicine Press Ltd. 2008: 3–11.
- Wollmann JC. The history of sclerosing foams. *Dermatol Surg* 2004; 30: 694–703.
- Wright D. Safety and Function of Sclerosant Foams. *American College of Phlebology 20<sup>th</sup> Annual Congress*, November 6–9, 2006, Ponte Vedra Beach FL, USA.