An Investigation into the Influence of Various Gases and Concentrations of Sclerosants on Foam Stability

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BACKGROUND Foam sclerotherapy is an increasingly popular modality in varicose vein treatment. Our previous work showed that the half-life of room air foam varied according to the percentage and type of sclerosant solution.

MATERIALS AND METHODS A plastic connector was used to create foam made from a combination of 0.25%, 0.50%, and 1% sodium tetradecyl sulfate (STS) and room air, carbon dioxide (CO₂), oxygen (O₂), or a mixture of CO₂ and O₂. To measure foam stability, the foam half-life was defined as the time it took for half the original volume of sclerosing solution to settle.

RESULTS Half-life varied according to sclerosant concentration when room air, O₂, or a mixture of CO₂ and O₂ was used for foam creation but not when CO₂ was used. Room air foam is more than 3 times as stable as CO₂ foam and 1.5 times as stable as a mixture of CO₂ and O₂.

CONCLUSIONS CO₂ foam half-life did not vary according to sclerosant solution concentration, though room air, O₂, and CO₂/O₂ did. The half-life of room air foam is more than 3 times as long as that of CO₂ and 1.5 times as long as that of a mixture of CO₂ and O₂. Foam half-life for room air and O₂ are similar at low concentrations of STS but differ at higher concentrations.

Portable Medical Devices, Inc., North Fort Myers, Florida, provided CO₂mander for testing.

Initially, sclerotherapy was performed using solutions (liquids) to promote sclerosis of the vein wall through a controlled phlebitic reaction. In the past few decades, foam sclerotherapy, created from mixing room air with the sclerosant solution, has become increasingly popular. Foam sclerotherapy has the advantage of higher efficacy rates because of longer contact time between the sclerosant and the vein wall. There are no statistically different rates of adverse events between foam and liquid sclerotherapy. Foam-specific side effects occur at distant sites, are rare, and include cough, chest tightness, dizziness, and visual disturbances.¹

Although the majority of phlebologists use room air for foam preparation, carbon dioxide (CO₂)² or a 70% CO₂/30% oxygen (O₂) mixture can also be employed.³ Our previous work showed that the half-life of room air foam varied according to the concentration of sclerosant solution.⁴ We sought to investigate whether the half-lives of foams made with CO₂, O₂, and CO₂/O₂ varied according to the concentration of sclerosant solution and to compare the half-lives of foam made from room air, CO₂, O₂, and CO₂/O₂.

Methods

Foam half-life was measured using a BD Safety Lok 3-mL syringe, a BD 5-mL syringe (Becton, Dickinson and Company, Franklin Lakes, NJ), and a B. Braun Adapter W/W connector (Melsungen, Germany). Room air, composed of 78% nitrogen, 21% O₂, and 1% of trace gases (CO₂, argon, neon, methane, helium, krypton, hydrogen, and xenon), was used as a control. Medical grade CO₂ and a nonmedical grade 77% CO₂/23% O₂ mixture, were obtained using a CO₂mander portable medical-grade CO₂ delivery system (Portable Medical Devices, Inc., North Fort Myers, FL). Medical grade O₂ was obtained from an O₂ cylinder tank (Western Medica, Westlake, OH). Sodium
tetradecyl sulfate (STS; Sotradecol, Bioniche Pharma, Belleville, ON, Canada) was selected because it is the only sclerosant that the Food and Drug Administration has approved for sclerotherapy. New sterile syringes and connectors were used for each trial so that decreasing silicone content in the syringe would not occur with subsequent trials.

**Foam Creation with Room Air**

The following standardized technique was employed throughout the study to create foam and determine exact foam half-lives. A sterile 3-mL syringe was used to draw up 1.0 mL of 0.25%, 0.5%, or 1% STS sclerosant and was connected to the end of a B. Braun Adapter W/W connector. Next, the syringe plunger was advanced forward until all air had been displaced from the syringe and adapter (Figure 1). A sterile 5-mL syringe with 4 mL of predrawn air was attached to the other end of the connector. Using the double-syringe system (DSS) technique, the 5-mL syringe was pushed to empty the 4 mL of air as much as possible through the connector to the 3-mL syringe with the sclerosant. This action was counted as one pump. Immediately thereafter, the room air–sclerosant mixture in the 3-mL syringe was emptied through the connector to the 5-mL syringe. This action was counted as two pumps. The to-and-fro cycle was repeated for a total of 10 pumps. At completion of the 10 pumps, a homogenous white foam was created (Figure 2) and filled the 5-mL syringe.

**Foam Creation with CO₂**

A sterile 3-mL syringe was used to draw up 1.0 mL of 0.25%, 0.5%, or 1% STS sclerosant and was connected to the end of a B. Braun Adapter W/W connector. Next, the syringe plunger was advanced forward until all air had been displaced from the syringe and adapter. A sterile 5-mL syringe was connected to the CO₂mmander system, and 4 mL of CO₂ was withdrawn under 10 pounds/inch² (Figure 3). This syringe was then connected to the other end of the B. Braun Adapter W/W connector. Using the DSS technique, a homogeneous white foam was created using the same technique as above.
Foam Creation with O₂

For the sake of completeness, the effect of O₂ on foam stability was also investigated. A sterile 3-mL syringe was used to draw up 1.0 mL of 0.25%, 0.5%, or 1% STS sclerosant and was connected to the end of a B. Braun Adapter W/W connector. Next, the syringe plunger was advanced forward until all air had been displaced from the syringe and adapter. A sterile 5-mL syringe was connected to the O₂ tank and 4 mL of O₂ was withdrawn. This syringe was then connected to the other end of the B. Braun Adapter W/W connector. Using the DSS technique, a homogeneous white foam was created using the same technique as above.

Foam Creation with 77% CO₂/23% O₂ Mixture

A sterile 3-mL syringe was used to draw up 1.0 mL of 0.25%, 0.5%, or 1% STS sclerosant and was connected to the end of a B. Braun Adapter W/W connector. Next, the syringe plunger was advanced forward until all air had been displaced from the syringe and adapter. A sterile 5-mL syringe was connected to the CO₂mander system, and 4 mL of CO₂/O₂ was withdrawn under 10 pounds/inch² (Figure 3). This syringe was then connected to the other end of the B. Braun Adapter W/W connector. Using the DSS technique, a homogeneous white foam was created using the same technique as above.

Measuring Foam Stability

The foam-filled 5-mL syringe was placed exactly vertical to the rubber stopcock of the 5-ml syringe on the bottom. The timer was started. Over the course of time, as the foam degenerated back into its constituents, the sclerosing solution was found to gradually re-form at the bottom of the syringe. When the bottom of the solution’s meniscus attained a volume of exactly 0.5 mL (half of the original sclerosing volume of 1.0 mL), as measured according to the graduations on the side of the syringe, the timer was stopped, and the time was recorded in seconds (Figure 4). Three sets of recordings were obtained and were averaged for each concentration.
of STS sclerosant used. All recordings were performed at an ambient room temperature of 20°C.

Results

The results are summarized in Table 1. The mean time for foam stability using room air was 85.7, 89, and 90.7 seconds with 0.25%, 0.5%, and 1% STS, respectively. The mean time for foam stability using CO₂ was 25.3, 25.7, and 28.3 seconds; using O₂ was 85.7, 79, and 73 seconds; and using a mixture of CO₂ and O₂ was 54.3, 58, and 49.7 seconds, at 0.25%, 0.5%, and 1% STS, respectively.

After three sets of recordings for each STS concentration in the four arms of the study, it was found that the foam half-life was 3 times as great with room air as with CO₂ group and 1.5 times as great with room air as with the mixture of CO₂ and O₂. There were no differences in room air and O₂ foam half-lives with 0.25% STS, but differences were seen at 0.5% and 1% STS. Although there was a significant increase in room air foam stability, with increasing concentrations of STS, this relationship did not occur with the CO₂ or CO₂/O₂ foam. O₂ foam half-life decreased with increasing concentrations of STS.

Discussion

Foam sclerotherapy is more efficacious in sclerotherapy because of longer contact time of the sclerosant with the endothelial cells. The majority of phlebologists use readily available room air for foam creation in sclerotherapy, although CO₂² and physiologic mixtures of 70% CO₂/30% O₂³ are becoming increasingly popular. Foam bubbles produced via turbulent flow using the Tessari technique and the double syringe system are smaller than the bubbles produced using the Monfreux technique. This smaller bubble size is associated with greater surface area of sclerosant, so a greater amount of sclerosant can be delivered to the endothelial cells.⁵ Bubble size is inversely related to the difference in density between a liquid and gas, as represented in the below equation.⁶

\[ dp = \left( \frac{6d_o \sigma}{\Delta \rho g} \right)^{1/2} \]

\( dp \) is bubble diameter, \( d_o \) is orifice diameter, \( \sigma \) is surface tension, and \( \Delta \rho \) is the difference in density between a liquid and gas. CO₂ and O₂ are 1.5 times and 1.14 times as dense, respectively, as room air. Therefore foam bubbles prepared from CO₂, O₂, or

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<th>TABLE 1. Foam Stability with Gases</th>
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<td>Percentage of Sodium Tetradecyl Sulfate</td>
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a combination of CO₂ and O₂ are smaller than those from air.

Laplace’s law states the pressure difference between the inside and outside of a bubble is inversely proportional to the bubble radius.

\[ \Delta P = \frac{P_i - P_o}{r} = \frac{2\gamma}{r} \]

\( P_i \) is pressure inside the bubble, \( P_o \) is pressure outside the bubble, \( \gamma \) is surface tension, and \( r \) is the radius of the bubble.

Therefore smaller bubbles, such as CO₂, disintegrate more quickly than larger bubbles because of a greater pressure gradient. Nitrogen is less dense than air and would therefore result in larger bubbles, and we hypothesize a longer foam half-life than with room air.

Foam composition, foam volume, and injection technique affect foam stability. Liquid sclerosant to gas ratios of 1:4 (1 part liquid to 4 parts gas) or 1:5 (1 part liquid to 5 parts gas) have been found to produce the most stable foams. CO₂ foam bubbles disintegrate quickly, and this effect is more pronounced as the ratio of sclerosant to gas is increased. The following equation describes foam stability in vivo.

\[ TP = \frac{r^2d}{2DSf} \]

\( TP \) is time of bubble persistence, \( r \) is radius, \( d \) is air density inside the bubble, \( D \) is the gas diffusibility through the bubble, and \( Sf \) is the saturation factor of gas in blood.

CO₂ has much greater diffusibility into blood than nitrogen (the dominant gas in room air), and, as a result, the half-life foam is shorter for CO₂. The diffusibility of CO₂ into blood is 19 times as high as that of O₂, as Graham’s Law, which states that diffusion rate of a gas through a liquid is proportional to gas solubility in a liquid and inversely proportional to the square root of the density of the gas, expresses.11

Silicone coating is present in syringes and syringe connectors to provide lubrication, but silicone is an anti-foaming agent. Prior studies by Rao and Goldman4 and Lai and Goldman12 have shown that the amount of silicone in syringe connectors does not affect foam stability, although foam stability varies between syringe manufacturers because of differences in the silicone content of syringes between manufacturers.

Our previous work showed that the half-life of room air foam varied according to the percentage of sclerosant solution. In our current study, we showed that the half-life of CO₂ foam did not vary according to the concentration of sclerosant solution, although room air, O₂, and a combination of CO₂ and O₂ did. Although the half-lives of room air and CO₂/O₂ increased with increasing concentrations of sclerosant, we were surprised to find that the half-life of O₂ foam decreased with increasing concentrations of STS. We also found that the half-life of room air foam is more than 3 times as long as that of CO₂ and 1.5 times as long as that of CO₂/O₂. There were no differences in the half-lives of room air and O₂ foam with 0.25% STS, although differences were seen with 0.5% and 1% STS.

A recent study in incompetent great saphenous veins treated with ultrasound-guided foam sclerotherapy created from CO₂ versus room air demonstrated fewer incidences of foam bubble–related side effects, including visual disturbances, chest tightness, cough, and dizziness, with CO₂-generated foam. One can speculate that the decreased upstream foam-related side effects are attributable to the short half-life of CO₂ foam. Further randomized controlled studies are needed to investigate whether efficacy varies between room air, CO₂, and a combination of CO₂ and O₂ in foam sclerotherapy.


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COMMENTS

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ALESSANDRO FRULLINI, MD*

Alessandro Frullini, MD, has indicated no significant interest with commercial supporters.

The article from Peterson and Goldman is valuable for the clear demonstration of the differences between different types of foam. This is an important point because the comparison of different experiences is often made notwithstanding the evident differences between techniques of treatment.

In addition, the problem of bubbles and gases used for foam generation has been greatly overemphasized. My recent studies on high endothelin levels after foam sclerotherapy (Proceedings of “Sclerotherapy 2010,” Bologna, Italy, March 26–27) clearly demonstrate that the cause of visual and neurological disturbances may be related to a different pathogenesis. It has been demonstrated that endothelin provokes vasospasm in the cerebral and retinal vessel, and the very high peak concentration after foam sclerotherapy may be the cause of such side effects.

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