

Scintigraphy-based analysis of possible pulmonary lesions after foam sclerotherapy: a pilot study

Lorenzo Tessari,¹ Marcello Izzo,² Attilio Cavezzi,³ Francesco Zini,⁴ Mirko Tessari,⁵ Daniela Grigolato⁶

¹Glaucio Bassi Foundation, Trieste;

²Mathematics for Technology, Medicine & Biosciences Research Center, University of Ferrara; ³Eurocenter Venalinfa, San Benedetto del Tronto (AP); ⁴Casa di Cura Città di Parma, Parma; ⁵Vascular Disease Center, University of Ferrara;

⁶UOC of Nuclear Medicine, University Hospital of Verona, Italy

Abstract

The aims of this study were to assess extemporaneous *in vivo* binding between $^{99m}\text{TcO}_4^-$ and two sclerosant detergents in foam sclerotherapy, and subsequently to control any possible damage in lungs and other organs related to sclerosant foam passage. A prospective comparative pilot study was performed on two male patients (62 and 56 years old) affected by varicose veins; each of them underwent scintigraphy investigations with free radiotracer and a scintigraphy investigation after each of the four sessions of sclerotherapy of varicose tributaries of the lower limbs with labeled sclerosant foam. One of the two patients underwent two further scintigraphic investigations, with free radiotracer and with labeled sclerosant foam, at a later stage. Four mL of 2% polidocanol (POL) foam, or four mL of 1% sodiumtetradecylsulfate (STS) foam for session were injected. The sclerosant foam was labeled with the radioactive tracer technetium pertechnetate, $^{99m}\text{TcO}_4^-$ (120 MBq per exam). Two scintigraphy assessments for free tracer (basal) and five scintigraphy investigations of bound-to-sclerosant tracer uptake/transit were obtained. No relevant variations in time/activity curves of the lungs and other organs were documented between the basal and post-sclerotherapy findings, also at the later stage. Free radiotracer mean region-of-interest data were: 336 counts (heart), 208 counts (lungs) and 371 counts (thyroid). Mean values extrapolated from each curve at each step for labeled CO_2O_2 -based sclerosant foam were respectively: 351 counts (POL) and 328 counts (STS) for heart, 202 counts (POL) and 188 counts (STS) for lungs, 335 (POL) and 263 (STS) for thyroid. No pulmonary damage by sclerosant foam was caused. Neither immediately after treatments, nor at short-term follow-up.

Introduction

Foam sclerotherapy was introduced more than 60 years ago, and Cabrera and Monfreux's innovative methods in the late 1990s gave a new impulse to using sclerosant foam (SF).¹ The extended use of this treatment was achieved after the introduction of the Tessari method.^{2,3}

Foam sclerotherapy has proved to be a validated, effective and safe method to treat varicose veins of the lower limbs,⁴ and possibilities and limitations for this technique have been elucidated in several publications.^{5,6} More recently, issues have been raised and discussed as to potential risks, side effects and complications of SF.⁷ Distal embolization of SF bubbles to lungs and possible lung capillary/parenchyma inflammation has been postulated in the past⁸ and recent⁹ literature. Furthermore, especially in the presence of a right-to left shunt such as a patent foramen ovale, isolated cases of neurological complications have been reported.⁴

The authors aimed to assess any possible change in the tissues of various organs, particularly the lungs, which may be affected by possible passage/impact of SF bubbles. Furthermore, any difference between air-based SF and CO_2O_2 -based SF was investigated in order to assess a possible higher safety profile of biocompatible gases *vs* room air. Finally, the clinical and experimental trial aimed at assessing any difference between the two commonly used detergent sclerosant drugs [sodiumtetradecylsulfate (STS) and polidocanol (POL)] as to the above-mentioned issues. In order to get a reproducible and quantifiable method for detecting possible tissue changes in the target/transit organs after sclerosant foam injections, scintigraphy was employed in a qualitative and semi-quantitative way. On the basis of the chemical/physical properties of pertechnetate ion ($^{99m}\text{TcO}_4^-$), a protocol to assess extemporaneous *in vivo* binding between $^{99m}\text{TcO}_4^-$ and POL/STS foam during various steps was designed. P

$^{99m}\text{TcO}_4^-$ shows a stable chemical structure not easily suited to bind other molecules. The study aimed at assessing the possibility of linkage between this radiotracer and the SF to check the presumed possibility of tracing the pathway and accumulation of SF bubbles by means of $^{99m}\text{TcO}_4^-$, as reported in a previous publication.⁸ In fact, in the vascular stream Pertechnetate ions remain in equilibrium, partially in free form and partially bound to serum proteins. More specifically, free ions leave the vascular compartment and migrate to interstitial fluids as a result of their small size, so as to decrease the pertechnetate blood concentration. This leads to an equivalent

Correspondence: Lorenzo Tessari, via Giovanni Falcone 24/B, Peschiera del Garda (VR), 37019 Italy.

Tel.: +39.0456401681.

E-mail: lorenzo@tessaristudi.it

Key words: foam sclerotherapy, scintigraphy.

Contributions: LT, study design, data collection, data analysis, critical review, final approval; MI, data analysis, critical review, final approval; AC, data collection, data analysis, writing, critical review, final approval; FZ, data collection, data analysis, final approval; MT, data collection, final approval; DG, data analysis, critical review, writing, final approval.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 24 April 2014.

Revision received: 23 September 2014.

Accepted for publication: 24 September 2014.

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Veins and Lymphatics 2014; 3:4037
doi:10.4081/vl.2014.4037

release of $^{99m}\text{TcO}_4^-$ that is bound to the proteins as an unavoidable result of its elimination.¹⁰ The Pertechnetate ion is removed by various organs and systems into the interstitial liquid, as seen in the stomach, thyroid, salivary glands, bowel, choroid plexus, kidneys, vascular structures and mucosae.¹¹ Interestingly, the pertechnetate ion is strongly taken up by the thyroid gland only in its free form and not bound to other molecules.¹²

Noticeably, lungs represent a transit organ for $^{99m}\text{TcO}_4^-$ and its temporal concentration peak declines along the 30 min of the scintigraphic observation and this pattern is very similar also for other various organs.¹³ Finally and more importantly, the increased capillary permeability leads to an increased $^{99m}\text{TcO}_4^-$ uptake in inflamed tissues. Therefore, in the case of possible drug-induced lung damage following foam sclerotherapy, there would be an increased $^{99m}\text{TcO}_4^-$ persistence into the lungs after its injection during the post-treatment period.

Materials and Methods

A prospective comparative pilot study was performed on two male patients (56 and 62 years old) affected by primary varicose veins (C2 of CEAP - Clinical-Etiology-Anatomic-Pathophysiologic - classification) related to

great saphenous vein (GSV) reflux. The patients were treated with SF which was labeled with a radionuclide ($^{99m}\text{TcO}_4^-$) and they gave informed written consent to the procedures; no ethical committee approval was required, as per any observational study in Italy. Basal scintigraphy was performed immediately after injection of 4 mL of saline solution with the radiotracer (RT) $^{99m}\text{TcO}_4^-$ in a varicose tributary of the lower leg. Subsequently, scintigraphy was performed after each of the four sessions of foam sclerotherapy which were performed on each patient. An overall imaging of the outcomes is reported in Figure 1. Injections were performed into the tributaries and the GSV stems, tailoring each session according to the outcomes achieved, using 4 mL of 2% POL foam or 4 mL of 1% STS foam per session with the patient in the supine position. Sclerosant foam was obtained through Tessari's method² with one part of sclerosant drug (POL or STS) and four parts of gas (air or CO_2 70%+ O_2 30%). Prior to foam formation, the sclerosant drug was mixed with $^{99m}\text{TcO}_4^-$ (120 MBq per exam): more specifically 1 cc of POL 2%, or 1 cc of STS 1% were mixed with 0.2 cc of RT.

In more detail, the flow chart of the protocol for each patient was as follows:

- Step 1, basal scintigraphy examination after injection of free $^{99m}\text{TcO}_4^-$ (Figure 2).
- Step 2 at day 7, scintigraphy examination 10 min after POL 2% + air radiolabeled sclerosant foam injection (Figure 3A).
- Step 3 at day 14, scintigraphy examination 10 min after POL 2% + CO_2 radiolabeled sclerosant foam injection (Figure 3B).
- Step 4 at day 21, scintigraphy examination 10 min after STS 1% + CO_2 radiolabeled sclerosant foam injection (Figure 3C).
- Step 5 at day 28, scintigraphy examination 10 min after STS 1% + air radiolabeled sclerosant foam injection (Figure 3D).
- Step 6 at day 42, scintigraphy examination for one of the two patients during the 90 min following free RT injection and 90 min after STS 1% + air radiolabeled sclerosant foam injection (Figure 4). This final step was undertaken to assess any possible late lung (and thyroid) tissue change due to several/repeated foam sclerotherapy sessions, as in the previous steps.

Radiation exposition was controlled in each patient after every step and no limit-exceeding figure was recorded.

Uptake and transit of free RT and of sclerosant-bound RT were assessed in transit organs (lungs and heart) and in target organs (thyroid, salivary glands, stomach) with semi-quantitative scintigraphy by means of a double-head gamma camera and region-of-interest (ROI) investigation. All scans lasted 30 min except for the step 6 scan (90 min). All dynamic evaluations were focused on the

chest and neck, in anterior and posterior projections.

Ninety photograms (1800 s in total) were taken at intervals of 20 s every frame (matrix 128×128 pixel). The count per second in ROIs were plotted against time and the curves were fitted (counting out the initial transient phase).

Activity in the site of sclerosant injection was measured at different interval times (see above) and the total count was divided by the background activity registered in the contralateral leg.

Results

At step 1 after injection of pertechnetate ion, the two patients showed a typical pattern of RT distribution in all transit and target organs and more specifically the semi-quantitative calculations resulted in a mean half time of 57.26 s in the lung, 57.35 s in the heart and -138.68 s in the thyroid. The integrated areas between 9th and 30th min were 336 (heart), 208 (lung) and 371 (thyroid). For each patient at step 1, step 2, step 3 and step 4, step 5 the various ROI images (same size) and relative

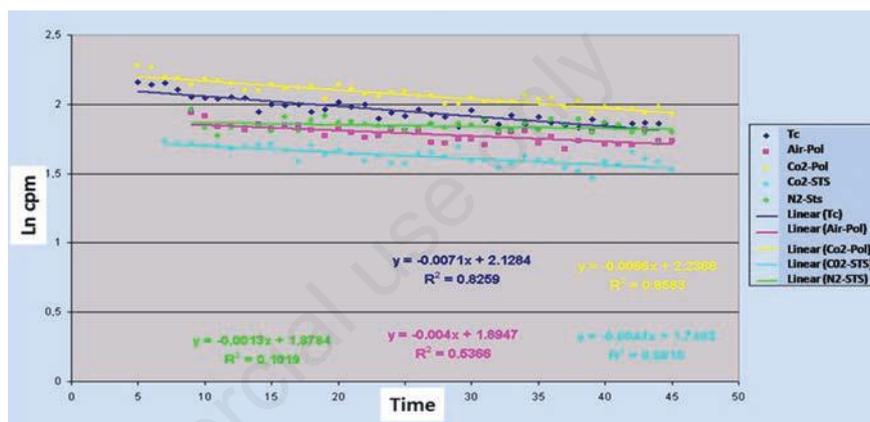


Figure 1. Curves and images of various regions-of-interest of different organ uptake after-free radiotracer injection (step 1).

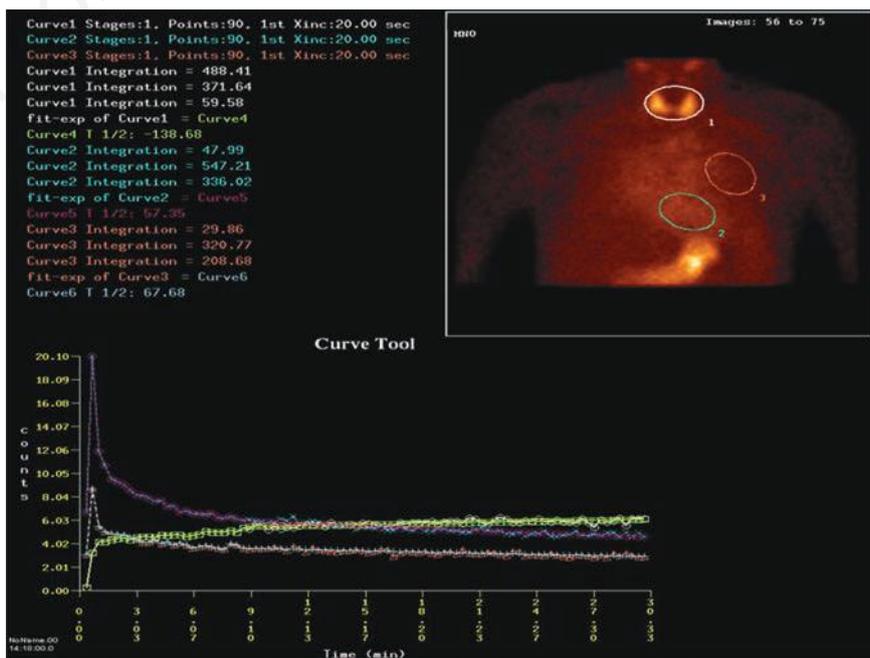


Figure 2. Organ uptake at step 1 for one patient.

curves of uptake have been summarized in Table 1 where mean figures for each organ and each session are summarized. The mean figures have been calculated for each organ after summation of all resulting values for each step and from both patients.

Comparison between step 1 and steps 2, 3, 4 and 5 showed overlapping time/activity curves related to lung transit. Assessment of overall amplitude of the curves showed a minimal difference in comparison to free RT curve related to the radioactivity which has remained trapped in the vessels of the leg which was the site of the sclerosant foam injection.

The only relevant difference between the basal step 1 and all other foam sclerotherapy steps (2 to 5) concerned the delayed transit time and a small reduction in amplitude in all samples, which is a consequence of peripheral vein uptake of the RT mixed with sclerosant foam. In fact, spasm of the treated vein and sclerosant foam stagnation in the treated veins (varicose tributary and consequently GSV trunk) contributed to the delayed arrival of RT to the lungs. Imaging of the varicose tributary and saphenous veins (Figure 5A) clearly depicted RT stagnation in these peripheral vein territories and gradual ^{99m}TcO₄⁻ release over time (Figure 5).

The activity/time curves related to the main up taking organs (thyroid and stomach in step 2,3,4 and 5) showed a pattern distribution which was overlapping the free RT curve of step 1. Data on these dose uptakes are summarized in Figure 1 and lung/thyroid/heart values are reported in Table 1.

As thyroid normally takes up ^{99m}TcO₄⁻ in its free form, the findings above highlight how RT in thyroid circulation is neither bound to the sclerosant bubbles nor to the sclerosant drug.

Examination of any possible difference in the patterns and curves for the two sclerosant drugs STS and POL at the four different sclerotherapy steps (2 to 5) in comparison to step 1 (free RT) showed overall similar results.

Conversely, air-based SF showed a more prolonged delay in time overall to reach the maximum radioactivity in the curves (time to max) in comparison to CO₂+O₂-based SF (Table 2).

We can speculate that bubbles of CO₂+O₂ sclerosant foam tend to break up earlier than air-based SF so that RT release is accelerated.

Data analysis of the procedures of step 6 in

one of the two investigated patients showed free ^{99m}TcO₄⁻ curves at the pulmonary and thyroid levels which overlap the step 1 activity/time curves (Figure 4). As no signifi-

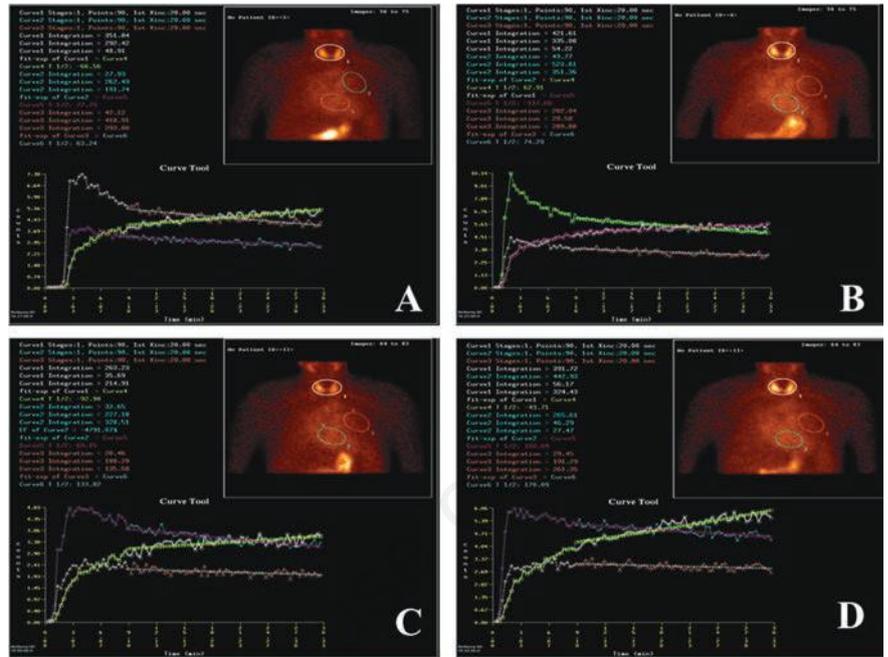


Figure 3. A) Organ uptake at step 2 for one patient; B) organ uptake at step 3 for one patient; C) organ uptake at step 4 for one patient; D) Organ uptake at step 5 for one patient.

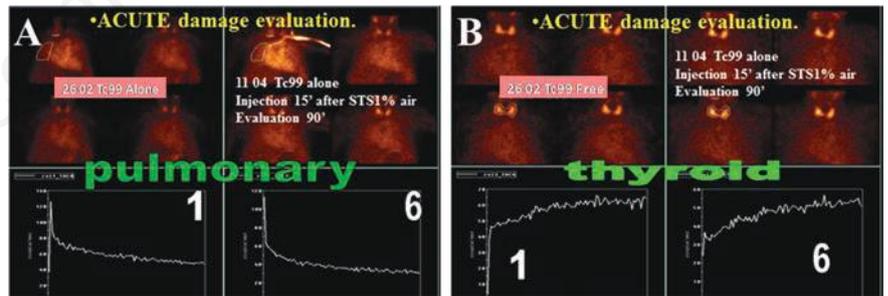


Figure 4. A) Step 6 images and curves of lungs after free radiotracer (RT) injection (left) and after last labeled sodiumtetradecylsulfate (STS) injection (right); B) step 6 images and curves of thyroid after free RT (left) and last labeled STS foam.

Table 1. Figures deriving from total counts in the different regions-of-interest between the 9th and the 30th min in each curve.

	Heart	Lung	Difference between basal (step 1) and sclerosant foam in lungs at step 2, 3, 4, 5	Thyroid
^{99m} TcO ₄ ⁻ (BASAL)	336.02	208.49	-	371.64
POL air	293.00	191.74	-9%	292.42
POL CO ₂ O ₂	351.36	202.04	-4%	335.08
STS CO ₂ O ₂	328.51	188.29	-10%	263.23
STS air	265.61	191.29	-9%	324.43

POL, polidocanol; STS, sodiumtetradecylsulfate.

cant difference in uptake was highlighted, these data confirm that at 42 days after four sclerotherapy sessions, no relevant changes in lung and thyroid circulation/tissues occurred.

Furthermore, the second part of step 6 consisted in one last foam sclerotherapy session with STS 1% sclerosant foam and subsequent scintigraphic assessment of RT uptake in the lungs and thyroid again showed no relevant changes in the curves in comparison to curves originating from free RT injection performed at the first part of step 6 (Figure 4).

As a consequence of these findings, no lung circulation changes due to sclerosant foam can be postulated.

The lack of important variations in the time/activity curves of the lungs between the first and the last foam sclerotherapy session indicates that sclerosant foam does not reach or does not induce any lung lesion.

Discussion

This observational experimental study was carried out to assess sclerosant foam effect on a few organs that may potentially receive a tissue lesion following sclerotherapy sessions.

After a preliminary investigation on technetium pertechnetate chemical-physical properties and on the possible binding interactions with SF, the authors finalized a clinical and scintigraphy protocol. The aim was to assess the pathway of SF bubbles/drug through the blood stream and the binding/effect of SF on target and transit organ tissues.

In a previous study,⁸ $^{99m}\text{TcO}_4^-$ was used to assess pulmonary patterns and bubble accumulation during foam sclerotherapy. In our study, the use of $^{99m}\text{TcO}_4^-$ proved to be unreliable to demonstrate the sclerosant drug pathway along the blood stream and within the transit organs (e.g. lungs), as the radiotracer flows independently. In fact, to bind the sclerosant drug to the ^{99m}Tc we would need an adequate procedure of reduction $^{99m}\text{TcO}_4^- + \text{Sn}^{2+} + \text{STS}$ or POL and hence the extemporaneous way to combine sclerosant drug with RT proved to be of no utility.

From the chemical and scintigraphy point of view, it is recognized that radionuclide ^{99m}Tc is obtained in physiologic solution as pertechnetate ion, and it has a coordination compound

among technetium and oxygen. The metal atom is bound to four binding oxygen (0-2) thus forming a very compact tetrahedron-like structure, with four identical faces of triangular shape.

Technetium oxidation state in ion is +7. This constitutes the most stable oxidation state and represents one of the most stable pertechnetate chemical species in watery solutions.

In order to prepare a radiolabelled drug from the $^{99m}\text{TcO}_4^-$, with coordinated bindings to give particular biological properties to the complex, it would be necessary to remove, partially or totally, the oxygen atoms that are bound to the metal. Finally substitution of these O_2 atoms with the coordinated atoms of new binders cannot happen with a simple extemporaneous mixing. Hence tracing SF pathway by means of this radiolabelled ion would require a more complex process to overcome the

chemical/physical difficulties as to above. Contrasting evidence from a few studies highlighted the possible alterations induced by the sclerosant foam on the lung capillaries/tissues. After a preliminary non-conclusive scintigraphic study from Milleret,⁸ on one side Grandi⁹ and collaborators showed lung parenchyma lesions in rats after foam sclerotherapy, on the other side Moro¹⁴ and co-workers recently showed no significant changes in pulmonary ventilation parameters after sclerosant foam injection.

One of the objective limitation of Grandi's study⁹ subsides in the injected dose of SF in the rats which was by far much higher than the maximum permitted dose in humans; similarly the very short time/pathway between ears (the injected site) and lungs may have influenced their conclusions as well.

Notwithstanding the very small sample size, the variability of the methodology (gas,

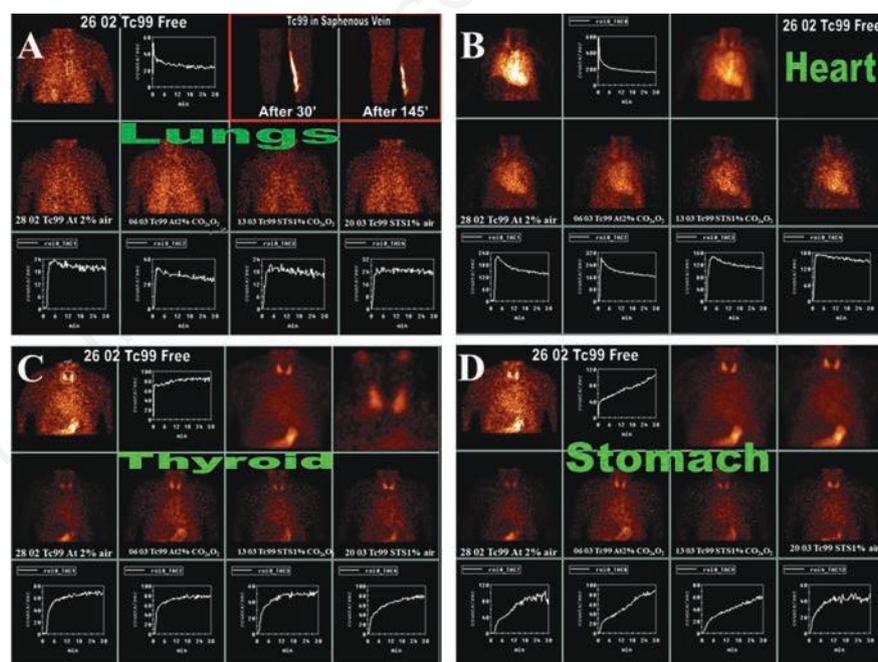


Figure 5. A) Lung and great saphenous vein imaging and lung uptake curves (for the first five steps); B) heart imaging and relative uptake curves (for the five steps); C) thyroid imaging and uptake curves (for the five steps); D) stomach imaging and uptake curves (for the five steps).

Table 2. Time to maximal radioactivity in each curve.

	Lungs	Heart	Thyroid	Background (vs contralateral limb)
$^{99m}\text{TcO}_4^-$	60 s	60 s	27 min	15 min
CO_2O_2 -based SF	120 s	120 s	17 min	19 min
Air-based SF	5 min	4 min	26 min	26 min

SF, sclerosant foam.

agents) and the limited pathology treated, this preliminary study confirms the overall safety of foam sclerotherapy as to the possible chemical lesion to transit/target organs. The invariable and total neutralization of STS or POL drug by blood components (proteins firstly) was demonstrated by Parsi¹⁵⁻¹⁷ and Watkins.¹⁸ Similarly Tessari and collaborators showed no free STS in the blood of common femoral vein (at short/mid/long term time intervals) after injecting STS-based sclerosant foam in the great saphenous vein/tributaries of the lower leg.¹⁹ Due to the very small sample size no statistical analysis was performed, though all data seem to be coherent with the conclusions on the safety of foam sclerotherapy as to the possible chemical lesion in distal transit/target organs.

Similarly no specific speculation on the possible foam bubbles accumulation in the lungs is possibly drawn from this study, as the mechanical passage of the SF bubbles was not quantified with this methodology; conversely the clinical/experimental study was addressed to investigate any possible residual lesion on the pulmonary capillaries/tissues after SF passage.

Though our investigations were aimed mainly at pulmonary circulation and no specific scintigraphic examination was carried out for brain/ocular circulation, the final total body scintigraphy of the second patient (step 6) did not show any residual lesion in any organs, including cerebral parenchyma.

The data from this observational study reinforce the concept of the absence of any direct chemical activity of SF within lungs and other central organs, which is coherent with the results of our scintigraphic study and with the results of other studies.¹⁵⁻¹⁹

Conversely all scintigraphic investigations showed a clear increase of RT accumulation in the injected areas of the lower limbs, where inflammation and sclerothrombosis obviously occurred.

Conclusions

A few conclusions may be drawn from the data collected through this scintigraphy-based

preliminary study: i) definitely no damage of the sclerosant foam on the pulmonary tissues was demonstrated; ii) extemporaneous mixing of a sclerosant drug with pertechnetate ion is not a correct procedure to highlight the drug pathways in foam sclerotherapy, differently from what was shown in the past; new, alternative procedures for a stable binding between STS/POL and RT would be required if the sclerosant drug tracing within the blood stream is targeted; iii) little delayed uptake differences were shown as to the time/curves between free RT and SF, due to the sclerosant foam transient persistence in the peripheral vein where it was injected; iv) air-based sclerosant foam top radioactivity was reached later than CO₂+O₂ based SF, due to the early release of the RT from the bubbles in the second case; v) no significant differences were highlighted between POL and STS curves.

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