

Optimizing CT lymphangiography: Insights from fluid dynamics

Purpose or Learning Objective

The importance of the lymphatic system and its associated disorders has long been underexposed. Advancements in lymphatic imaging, particularly the intranodal delivery of contrast agents, have enhanced our understanding of the central lymphatic system, and enabled the study of its pathological aspects, including locating disruptions.

An initial animal study successfully established the optimal CT lymphangiography (CTL) protocol for enhancing the thoracic duct in micromini pigs. Since then, CTL emerges as a promising technique, offering rapid, anesthesia-free imaging, broader patient eligibility, and increased accessibility. However, challenges in the contrast enhancement of the central lymphatic system have surfaced during the clinical implementation of CTL. The fluid dynamics of contrast agents are thought to play a crucial role in the success of lymphatic imaging. Therefore, **the primary objective of our study is to clarify the challenges encountered in clinical application of CT lymphangiography by exploring the flow dynamics of iodinated water-based contrast in lymph analogues with varying viscosity and density.**

Methods or Background

Description of clinical challenges

Patients with a clinical suspicion of acquired or congenital central lymphatic flow disorder and unable to undergo MR imaging underwent CTL between June 2020 and June 2023 at the Radboud university medical center due to. All CTL scans were performed using a 320-slice CT scanner. A standardized scoring system was used to assess the contrast enhancement of the thoracic duct, visibility of fluid collection and the identification of any thoracic duct leakage.

Clarification of clinical challenges through flow-dynamics

A 320 mm CTDI phantom model was employed to facilitate thorough investigation. To mimic lymphatic vessel dynamics, a 3D-printed 3 mm \varnothing hard resin tube was used alongside a fluid simulation system, using two 60 ml double syringe pumps (Aladdin syringeTWO [AL-40 [AL-4000]]), one for the lymphatic fluid analogue and one for the contrast agent. Lymphatic fluid was mimicked using a water-glycerol analogue with varying viscosity (0.85 - 2.2 cP) and density (997 – 1044 kg/m³) to replicate individual variation. The analogue was pumped through the phantom at a fixed velocity of 8.46 ml/min, alongside a contrast agent at a velocity of 1 ml/min. For the contrast agent different concentrations between 56-400 mgI/mL were used with added red dye (approximately 10 μ L), allowing for qualitative assessment of contrast flow dynamics. To simulate TD leakage, a second tube included a 1.5 mm \varnothing hole. Figure 1 illustrates the schematic overview of the model.

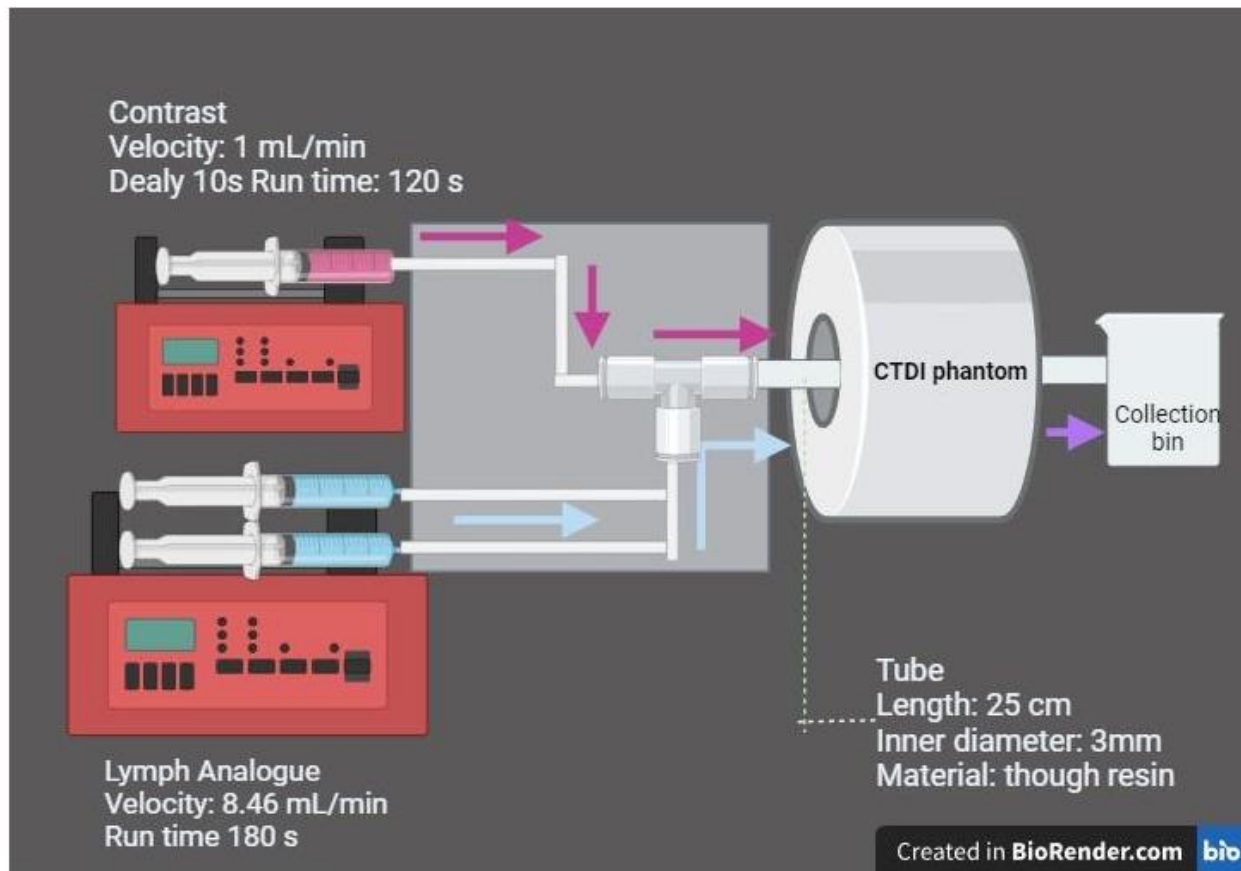


Figure 1 | Schematic overview of the phantom model used during this experiment

Qualitative assessments include visual observations of contrast flow dynamics, exploring combinations of liquids replicating lymphatic fluid analogue and contrast agent behavior. Quantitative assessment involved plotting the systematically measuring HU values at specific time intervals. Afterwards, a trendline was fitted to represent the curve and differences between the trendlines of each contrast concentration was analyzed based on the maximum HU reached, start and end HU, and mean slope using independent T-tests. To estimate contrast propagation speed, mean HU over time is analyzed for specific slice pairs with a fixed distance of 150 mm between slices. Velocity calculations are performed for each contrast agent concentration. One-way ANOVA was used to analyze differences between contrast agent concentrations and to test for statistical significance ($p < 0.05$).

Results or Findings

Description of clinical challenges

Intranodal CTL was initially performed using iodinated contrast agents (Iomeron 400 (n=6) or 300 (n=6)) in patients with chylothorax or protein losing-enteropathy. These scans yielded unpredictable thoracic duct (TD) opacification, as full-length TD opacification was observed in 6/12 (50%) patients. Ten patients exhibited clinical signs of lymphatic leakage, either presenting as pleural leakage resulting in chylothorax or enteral leakage leading to protein-losing enteropathy (PLE), underwent CTL examination. The aim was to detect if the origin of the leakage was within the central lymphatic vessels, but such an origin was identified in only one patient. Figure 2 shows the representative image of the thoracic duct

and the site of the leakage in the patient. **In total, CTL provided adequate information to formulate a therapeutic plan in two cases, while the remaining ten patients required additional imaging.**

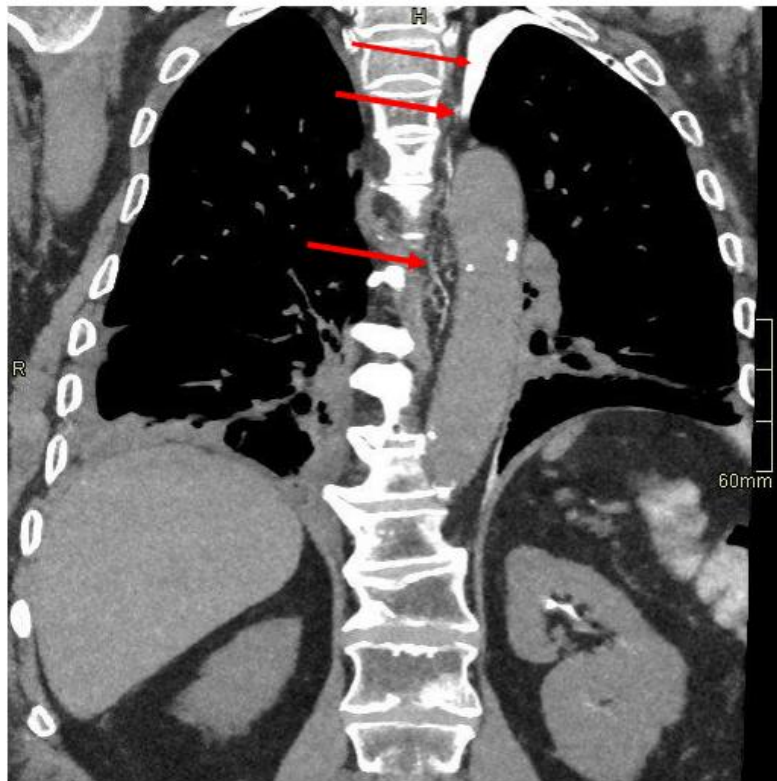


Figure 2 | Representative images of the thoracic duct and lymphatic leak identified in Patient 7.

Clarification of clinical challenges through flow-dynamics

Overall, contrast agents separated in the entire range of viscosity and density among lymph analogues. For example, the use of Iomeron 400 or Iomeron 300 resulted in sinking and accumulation behaviors in all variants of the lymphatic analogue, suggesting poor contrast agent transport and integration. When the dynamic properties of both the lymphatic fluid analogue and the contrast agent matched, better contrast integration was observed. This was achieved by diluting Iomeron 400 mgI/ml to 56 mgI/ml to match the properties of the lymph analogue fluid (1.5 cP and 1064 kg/m³).

Furthermore, quantitative assessments of Iomeron 400-150 mg I/ml found decreasing HU along the length of the tube. Statistical analysis on the slope of the different trendlines, representing the voxel values over the length of the tube and over time, demonstrated that there were significant differences between contrast agents. Independent t-tests showed significant differences in the mean slope of the curve between Iomeron 300 and 250, Iomeron 300 and 150, and between Iomeron 250 and 150.

The observations of the qualitative and quantitative assessment showed that the behavior of contrast agents varied depending on the combination of lymphatic fluid analogues and contrast agents used. **The results suggest poor contrast agent transport and integration when the dynamic viscosity and density of both the lymphatic fluid analogue and contrast agent do not match. Whereas better integration is observed when the dynamic properties of both fluids do match.**

Speed of contrast propagation

The pump was set at a velocity of 8.46 mL/min for the lymph analogue and 1 mL/min for the contrast agent. Therefore, the velocity of the lymph in the tube with a diameter of 3 mm is 22.63 mm/s. The mean speed of contrast propagation for Iomeron 400 was 11.67 (SD \pm 0.101), for Iomeron 300 18.96 (SD \pm 0.814) and for Iomeron 250 this was 19.23 (SD \pm 2.96). ANOVA indicates no significant difference between and among groups. However, **these results indicate that the propagation of the contrast agent is slower than the calculated velocity of the lymph analogue.** Due to noise, we were not able to assess the speed of contrast propagation for Iomeron 150 and 56.

Detection of the leakage site

This study introduced a model for the detection of lymphatic leakage. **The experiments showed that the location of a hole can impact the outflow of the contrast.** We noted variations in both outflow volume and the time to visualization when comparing the two scenarios: either with the hole at the dependent or the upper side of the tube. Resulting in respectively 18 seconds or 40 seconds before the contrast agent has exited the tube through the hole. Figure 3 illustrates an axial view of a leakage model. In the image on the left, the hole is at the dependent side and in the image on the right, the hole is facing upward. Both images are set to the same window width and window level settings. These snapshots were captured 88 seconds after initiation of the contrast agent. **This finding highlights that the location of the leaking point can influence the time to leakage visualization.**

Conclusion

These experiments collectively have shown that the fluid dynamics between lymphatic fluid and contrast agents can help clarify the challenges encountered in clinical applications of CTL. This study highlighted issues in achieving desired opacification of the thoracic duct, emphasizing the need for further research on lymphatic fluid properties, and enhancing both diagnostic and therapeutic strategies in lymphatic imaging. Matching the properties of contrast agents to those of lymphatic fluid **seems to** play a more prominent role in achieving the desired opacification and diagnostic quality than previously anticipated. **In particular, this research highlights the importance of the choice of contrast agent in the distribution and movement patterns within a tubular system.**

It is important to note the complexity of the lymphatic system and its variability among and within individuals. Lymphatic fluid properties can vary widely, and here we used two different analogue fluids as a simplification for lymph. Unfortunately, patient-specific research on lymphatic fluid properties is yet lacking.

Future research on the composition of lymph is needed to eventually improve the accuracy of lymphatic imaging techniques. Moreover, it could prove beneficial to consider other methods than normal visual evaluation of the radiological images, such as a three-dimensional reconstruction of the images. Eventually, optimizing the current protocols will allow for more precise and effective diagnostic strategies.

EPOS

This is to confirm that

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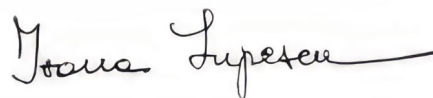
Optimizing CT lymphangiography: insights from fluid dynamics (C-16310)

within the framework of the Educational
and Scientific Programme at

ECR 2024
FEBRUARY 28 - MARCH 3, 2024



Professor Carlo Catalano
ESR President



Professor Ioana G. Lupescu
EPOS Coordinator