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Original Article

Visualising lymphatic flow dynamics during complex physical therapy: A photoacoustic imaging study

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ABSTRACT

Background: Complex physical therapy (CPT), which combines compression and exercise therapies, is the cornerstone of lymphedema treatment. However, assessing lymphatic flow in living humans is challenging owing to the small size and transparent nature of lymphatic vessels. Herein, we introduce a novel approach utilising photoacoustic imaging (PAI) to visualise lymphatic flow dynamics under CPT conditions. Compared with existing modalities, PAI offers superior details, enabling real-time evaluation of lymphatic vessels during compression and exercise. Real-time evaluation of lymphatic flow may enable advanced research on optimal perioperative compression therapy and exercise therapy.

Methods and Results: Herein, PAI was used to assess lymphatic flow in four healthy subjects. Detailed images of lymphatic and blood vessels were obtained using photoacoustic lymphangiography, which utilises indocyanine green as a light absorber. The participants underwent simulated compression using a transparent film dressing, with a pressure of approximately 20 mmHg. Exercise stress was applied to mimic CPT conditions. Compression

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facilitated the collapse of superficial veins while lymphatic vessels remained intact. Additionally, the lymphatic pumping frequency was the highest during combined compression and exercise, highlighting the synergistic effect of these therapies on lymphatic flow.
Conclusion: Our findings underscore the potential of PAI in elucidating the mechanisms underlying the efficacy of CPT. PAI may enable comprehensive assessments of vascular changes during CPT by allowing simultaneous delineation of veins and lymphatic vessels. While our study represents a significant step forward, its limitations, including small sample size and exercise regimen specificity, warrant further investigations.

Introduction

Complex physical therapy (CPT), which combines compression and exercise therapies, is one of the most common treatments for lymphedema.[1] However, it is difficult to assess lymphatic flow in living humans in detail because lymphatic vessels are transparent and small, making visualisation difficult. Thus, although CPT can lead to symptomatic improvements in congested lymphedema, assessing the actual flow of lymphatic fluid during CPT is challenging. We previously reported that detailed lymphatic flow can be visualised in vivo using a photoacoustic imaging (PAI) device, which can evaluate lymphatic vessels in greater detail than other existing modalities.[2–5] As this device can capture images during motion, the condition of the lymphatic vessels can be evaluated during compression and exercise, and the effects of CPT can be visualised. This study aimed to clarify lymphatic flow dynamics during CPT.

Method

Participants

Four healthy volunteers were enrolled, all of whom underwent the experiments; data were collected from the limbs of the participants. Written informed consent was obtained from all participants. This study was approved by the institutional ethics committee and the review board of our institution.

Photoacoustic lymphangiography (PAL)

PAL is a type of PAI for specifically imaging lymphatic vessels. Compared with existing techniques, such as near-infrared fluorescence contrast imaging, PAL enables more detailed imaging of lymphatic flow.[2–5] Herein, PAI-05 (Canon, Inc., Hitachi, Ltd., and Japan Probe Co., Ltd., Japan) was used to visualise lymphatic vessels. PAI-05 can noninvasively delineate optical absorbers, such as haemoglobin, to locate blood vessels in vivo in three dimensions.[6] However, because lymphatic fluid is transparent, it is not possible to delineate lymphatic vessels readily. Indocyanine green (ICG) can be used as a light absorber to identify lymphatic vessels. This makes it possible to delineate lymphatic and blood vessels simultaneously. PAI-05 captures multiple small images of a 2 cm^2 area, and the sensor moves around the imaging area and superimposes the images to obtain an imaging field of 180 × 270 mm. Additionally, images can be captured moving images by fixing the sensor site.

PAL was performed after ICG injection, for which ICG (5.0 mg) was dissolved in 5% glucose solution. In the lower extremities, ICG was subcutaneously injected into the first and fourth web spaces and the

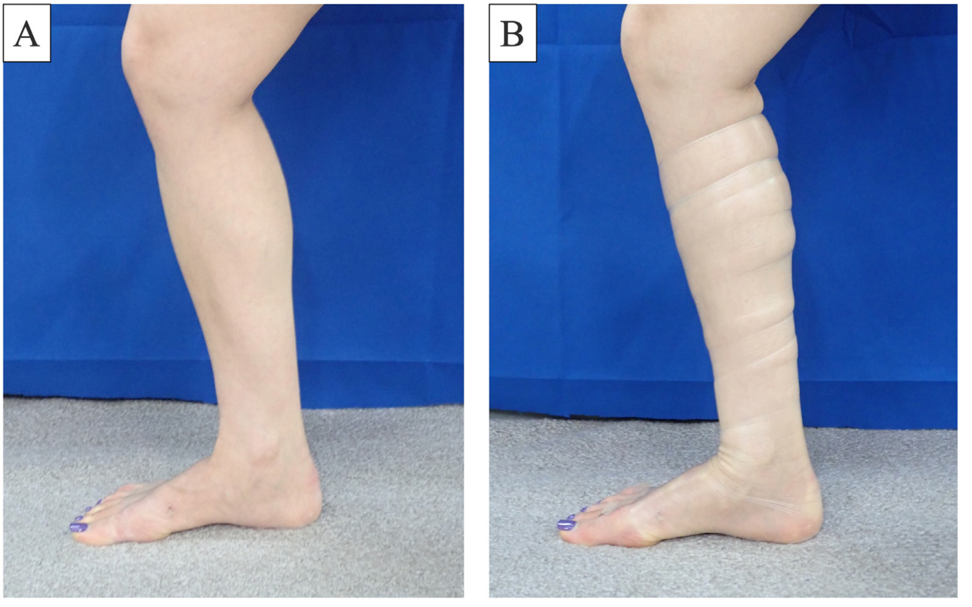

Figure 1. A transparent film dressing, Airwall® (KYOWA LIMITED, Japan), was used to simulate the compression environment.

lateral malleolus at a dose of approximately 0.2 mL. In the upper extremities, ICG was subcutaneously injected into the first and fourth webs and the palmaris longus tendon at the same dose.

Simulation of compression conditions

To simulate the compression environment, a transparent film dressing, Airwall® (KYOWA LIMITED, Japan), was used. The pressure was checked using PicoPress® (Microlab Elettronica, Italy), which was confirmed to be approximately 20 mmHg (Figure 1). Since the Airwall® is transparent, the laser light can reach the subcutaneous light absorber, and PAL can be performed.

Simulation of exercise stress

For the lower extremities, the medial leg was used, while for the upper extremities, the forearm was the site of capture. The ankles were lightly flexed and extended to simulate exercise for the lower limbs, and the hands were grasped and opened to simulate muscle movement for the upper limbs (Movie 1).

Results

Of the included participants, one was a man and three were women. The mean age of the participants was 33.0 ± 4.2 years.

Lymphatic vessels in a compression environment

Compression caused superficial veins to collapse, making it easier to visualise lymphatic vessels (Figure 2). This suggests that superficial veins may collapse quickly under mild pressure. In contrast, lymphatic vessels are maintained because of their relatively high pressure.

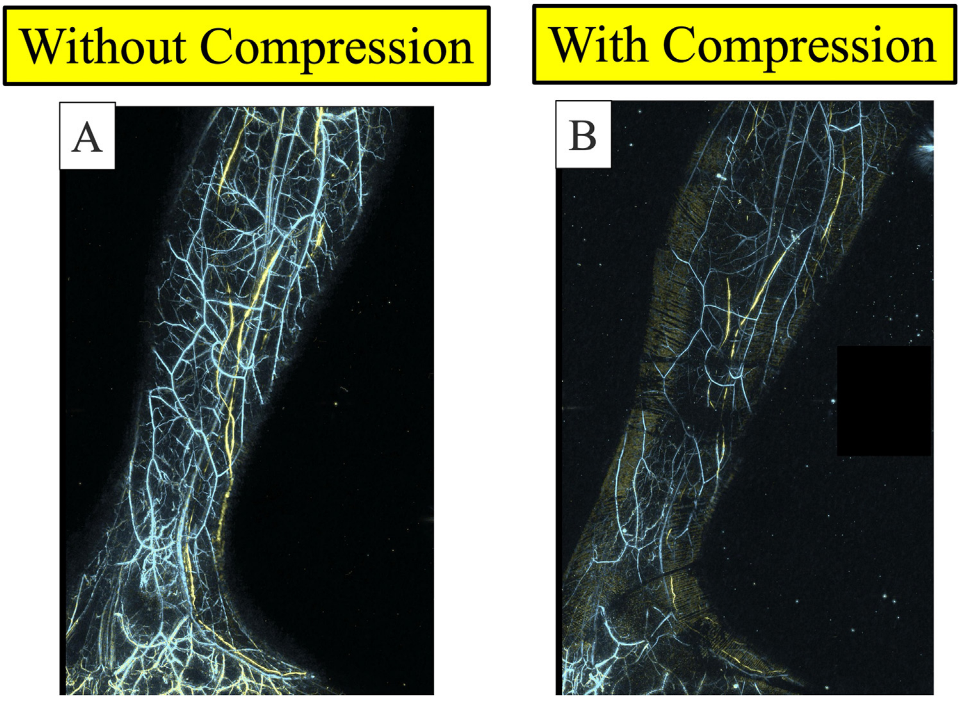

Figure 2. Compression caused superficial veins to collapse, making it easier to visualise lymphatic vessels.

Table 1
Lymphatic pumping frequency under different conditions.

	Without compression		With compression	
	Rest	Motion	Rest	Motion
No. of lymphatic pump (times/min)	0.6	0.4	0.2	1.4

Lymphatic vessels in a compression environment with exercise stress

In one participant, imaging could be performed during compression and exercise (Movie 2).

The participant was observed for approximately 5 min and the number of lymphatic pumps at the same site was evaluated. Lymphatic pumping frequencies were 0.6 times/min, 0.4 times/min, 0.2 times/min, and 1.4 times/min during resting, exercising, compression resting, and compression exercising, respectively. Lymphatic flow was best observed when compression was applied and exercise was performed (Table 1).

Discussion

CPT, a combination of compression, exercise under compression, lymphatic drainage, and skin care, is one of the most evidence-based treatment modalities for lymphedema. Methods for imaging lymphatic vessels include lymphoscintigraphy,[7] near-infrared fluorescence lymphangiography,[8–10] magnetic resonance lymphangiography,[11–13] and ultrasonography.[14,15] However, while lymphoscintigraphy allows the assessment of the entire lower limb, the details of individual lymphatic vessels remain unclear. Near-infrared fluorescence lymphangiography has the advantage of being able to assess lymphatic vessels in real time and is commonly used for preoperative lymphaticovenular anastomosis mapping. Magnetic resonance lymphangiography is expected to develop further in the future; its advantages include high-resolution three-dimensional imaging capabilities and a wide imaging range. However, it is currently difficult to delineate small lymphatic vessels and perform real-time imaging. Although dilated lymphatic vessels can be identified by ultrasonography, identifying other lymphatic vessels can be challenging due to issues with reproducibility and the skill of the practitioner.

Our photoacoustic imaging system has a resolution of 0.2 mm and can identify multiple parallel lymphatic vessels individually. In addition, veins can be simultaneously visualised, allowing the assessment of lymphatic flow during CPT, which has been difficult in the past.

Several studies have utilised existing methods to accumulate further evidence for CPT by assessing lymphatic regurgitation patterns after CPT or measuring lymphatic pressure and inferring the appropriate pressure for drainage.[16,17] However, these studies have been limited to indirect assessments and not direct imaging assessment during CPT.

Herein, the use of PAI enabled the simultaneous delineation of veins and lymphatic vessels, revealing how the vascular system changes under compression. We observed that under compression, superficial veins collapsed easily; however, lymphatic vessels were maintained. This may be attributed to the higher internal pressure of lymphatic vessels, at approximately 30 mmHg, compared to that of the veins.[18] Additionally, we observed that the frequency of lymphatic flow was higher when exercise stress was applied than when pressure was applied. Thus, we could reconfirm the importance of using the pumping action of large muscles in CPT, as previously suggested.[19,20]

This study has some limitations. First, it remains unclear whether the exercise simulation used herein reflects exercises used in CPT appropriately. Second, the number of participants was small. Further studies with larger numbers of participants are required.

Conclusion

Our study, utilising PAI, provides valuable insights into the dynamics of lymphatic flow under CPT conditions. By visualising lymphatic vessels in detail, we demonstrated how compression and exercise affect lymphatic flow. The real-time evaluation of lymphatic flow may advance research on optimal perioperative compression therapy and exercise therapy. Our study underscores the potential of PAI as a valuable tool for assessing the efficacy of CPT in treating lymphedema. Further studies may help optimise therapeutic interventions and improve outcomes in patients with lymphatic disorders.

Patient consent

Oral and written informed consent for participation in this study and publication consent were obtained from all participants.

Ethics approval

The study was approved by the Certified Review Board of Keio and Keio University School of Medicine Ethics Committee.

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Data sharing statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors have no competing interests.

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