

Experimental Drainage Device to Reduce Lymphoedema in a Rat Model

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WHAT THIS PAPER ADDS

Lymphoedema management currently relies on standard conservative treatments that include manual lymphatic drainage followed by compression strategies to contain the swelling. As lymphoedema is a chronic disease, it requires lifelong management with onerous consequences for patients' quality of life. The results presented here pave the way for an innovative treatment option that proposes to substitute the impaired lymphatic system with an implanted drainage device that would re-establish physiological drainage.

Objective: Despite recent advances in pharmacological research and microsurgery, lymphoedema remains an incurable disease that deeply affects quality of life. There is an urgent need for innovative approaches to restore continuous lymph flow in affected tissues. To this end, the efficacy of a subcutaneously implanted draining device in reducing lymphoedema volume in a rat hindlimb lymphoedema model was tested.

Methods: A rat model of chronic lymphoedema was developed by surgical removal of popliteal and inguinal lymph nodes, followed by irradiation. The model was characterised by monitoring limb volume via tape measure, skin water content via dielectric constant measurement, and lymphatic drainage via lymphofluoroscopy. After lymphoedema establishment in 16 Wistar rats, a device made of fenestrated tubing equipped with a miniaturised pumping system, was implanted subcutaneously in the affected limb to restore continuous recirculation of interstitial fluid.

Results: Lymphofluoroscopy imaging showed impaired lymphatic drainage following lymphadenectomy and irradiation. Affected limb volume and skin water content increased significantly compared with the untreated limb, with a median (interquartile range) of 3.85 (0.38) cm³ versus 3.03 (0.43) cm³ for volume ($n = 16$, $p = .001$) and 26.6 (9.1) versus 16.6 (3.7) cm³ for skin dielectric constant ($n = 16$, $p = .001$). Treatment of lymphoedema with the implanted drainage device showed that 5 weeks post-implant excess volume was significantly reduced by $51 \pm 18\%$ compared with the pre-implant situation ($n = 9$ sham group, $n = 7$ pump group).

Conclusion: Lymphoedema volume in the rat model was significantly reduced by restoring continuous drainage of excess fluid using a novel subcutaneously implanted device, opening the way to the development of an artificial lymphatic vessel.

Keywords: Implantable pump, Lymphoedema, Subcutaneous drainage

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INTRODUCTION

Secondary lymphoedema (LE) is a frequent chronic, yet underrecognised, disease characterised by the accumulation of interstitial fluid and macromolecules leading to tissue swelling. Cancer and cancer related interventions (i.e., surgery, radiotherapy) are frequent causes of LE occurring both in the upper and lower limbs.^{1–4} Currently, no curative treatment exists for LE, and management of patients is

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based mainly on chronic symptomatic therapy consisting of complete decongestive therapy, a combination of skin care, manual lymphatic drainage (MLD), decongestive exercises, and compression strategies aimed at reducing and then containing the swelling of the affected limb.⁵ Alternative treatments for LE are reconstructive and debulking surgical techniques.

Reconstructive surgery aims to restore lymphatic function with newly created lympho–venous or lympho–lymphatic bypass, with lympho–lymphatic venous segmental reconstruction, or by vascularised lymph node transfer.^{6–10} One interesting technique was recently developed, consisting of the subcutaneous implantation of silicone tubes with lateral access holes that create a draining route bypassing the region with non-functional lymphatic vessels.^{11,12} Compression therapy is needed to create the pressure necessary to drive the interstitial fluid into the silicone tubes.

Despite advancements in lymphatic surgery, complete decongestive therapy remains the standard of care, involving lifelong treatment that significantly impacts on quality of life.¹³ Patients not only need to attend frequent physiotherapy sessions, but they also need to wear heavy and cumbersome compression garments between sessions. The lives of patients with LE are affected by the continuous fear of skin infection (erysipelas), by the fact that LE represents a constant reminder of their treated cancer, and by a series of limitations at the social and personal level.^{14,15}

There is therefore an urgent and great need to develop innovative treatment strategies to improve the quality of life of patients with LE.

To this end, animal models closely reproducing the pathophysiology and progression of the disease are extremely important. Even though several animal models have been described in the past, there is still a lack of well characterised and reproducible models suitable to test among other treatments, surgical procedures. Models of LE in rabbits, dogs, and sheep have several limitations, including transient effect, high mortality, and no volume increase.^{16,17} Volume increase was reported in porcine models, but the LE observed was only acute.¹⁸ Currently the most reliable animal models of LE are developed in rodents, both in the hindlimb and in the tail. The tail model is useful to study the pathophysiology of the disease, and to test drug formulations and regenerative approaches, but it is unsuitable to test surgical procedures. The hindlimb model in rodents is the only model to show stable LE induction after lymphadenectomy and irradiation.^{19–21}

Based on these observations, the first aim of this study was to generate and verify the chronicity of the rat hindlimb LE model, based on the surgical removal of popliteal and inguinal lymph nodes, followed by irradiation of the inguinal area. The second aim was to test a novel technique to treat LE, based on active internal drainage of the excessive interstitial fluid. Using the rat hindlimb model, the feasibility of draining excess fluids and reducing LE using a unique,

subcutaneously implanted peristaltic pump connected to a drainage catheter placed in the oedematous tissue has been investigated for the first time.

MATERIALS AND METHODS

Rat hindlimb lymphoedema model

Female Wistar rats (250–300 g) were purchased from Charles River Laboratories (Saint-Germain-sur-l'Arbresle, France). Animals were allowed to acclimatise to their new environment for 1 week before the start of the experimental procedure. Animals were housed in conventional facilities and handled according to institutional regulations after ethical approval from the Office Vétérinaire Cantonale Vaud, Switzerland (authorisation VD2911). Experiments were conducted in accordance with Directive 2010/63/EU of the European Parliament. LE was induced in the left hindlimb by removal of popliteal and inguinal lymph nodes, followed by irradiation. The right hindlimb was left untreated and used as an internal control. Prior to surgery, rats received buprenorphine analgesia (Temgesic 0.05 mg/kg, subcutaneously). Anaesthesia was induced with isoflurane (4% for induction and 1–1.5% throughout the procedure). Lymphatic vessels were visualised by intradermal injection of 10 µL 10% Evans Blue (Sigma–Aldrich, Buchs, Switzerland) solution into the dorsum of the paw. Through a 2 cm skin incision, the groin fat pad was completely resected to remove inguinal lymph nodes. The popliteal lymph node was identified by Evans blue accumulation and excised. Internal sutures were used to close the scar. Healing was allowed over 1 week, during which rats received analgesia (buprenorphine for the first 2 days followed by 2 g/L paracetamol in drinking water) and during which they were monitored daily. One to two weeks after surgery, rats were positioned using a fluoroscan (Fig. S1; see Supplementary Material) and the inguinal area was irradiated under isoflurane anaesthesia with 22.7 Gy at 225 keV and 13 mA (X-RAD 225cx; Precision X-Ray, North Branford, CT, USA) administered with two opposing beams, antero-posterior and postero-anterior. The dose was prescribed at 10 mm depth and administered with a 40 × 40 mm square collimator. Irradiated skin was treated topically with Biafine emulsion for 3 days following irradiation. Bodyweight was monitored throughout the entire experiment. At the end of the experiment animals were euthanised with an intraperitoneal injection of at least 200 mg/kg sodium pentobarbital.

Monitoring of lymphoedema

Hindlimb oedema (volume) was calculated by truncated cone approximation. Limb circumference was measured at five different levels, 1–3 cm between the heel and the knee. The volume of the affected hindlimb was compared

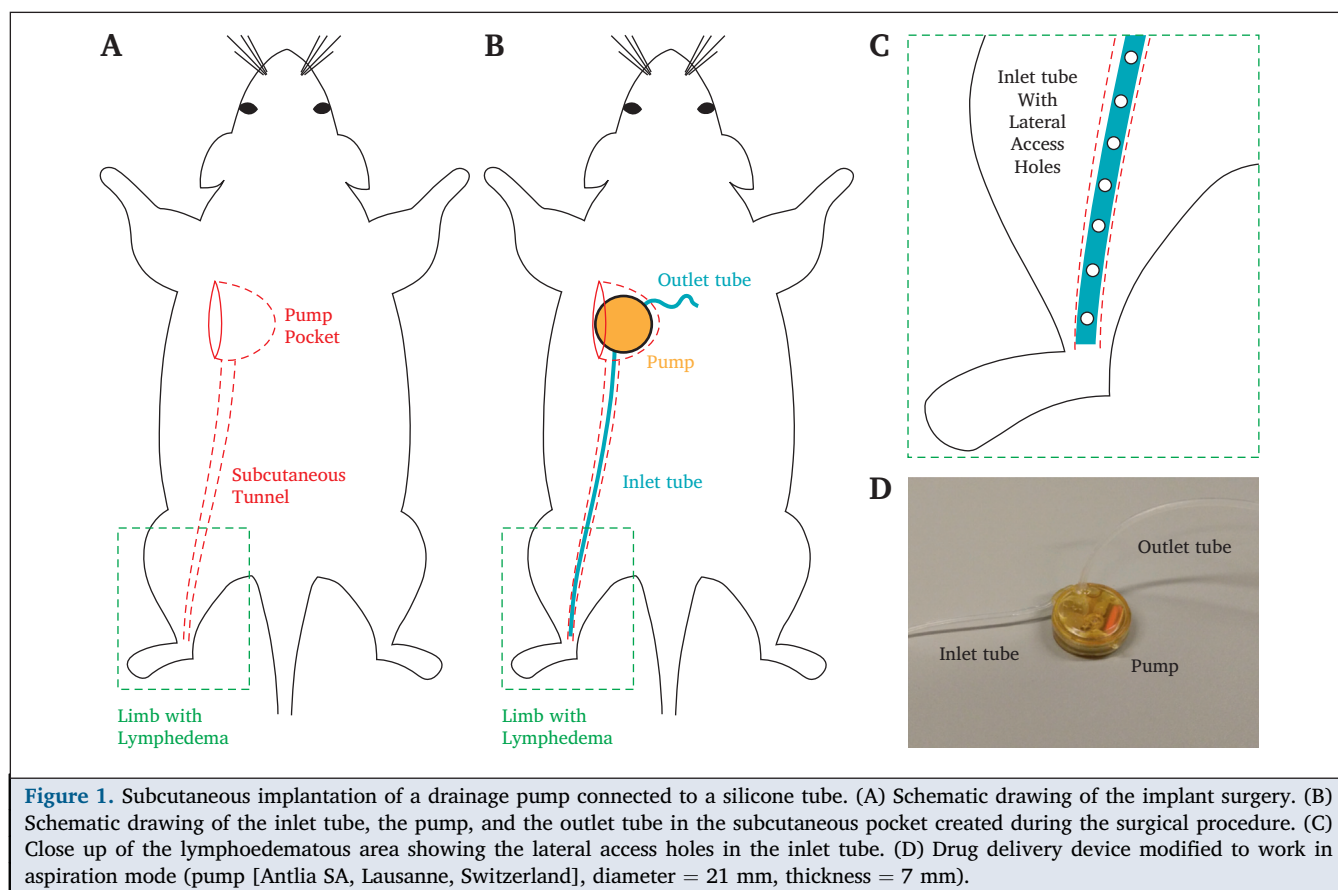
with the unaffected contralateral one. Skin dielectric constant, an indirect measure of water content, was measured using a moisture meter (MoistureMeterD [small probe]; Delfin Technologies, Kuopio, Finland) at three different anatomical locations: the dorsum of the paw, and the dorsal and ventral hindlimb.

Lymphofluoroscopy

At the end of the experimental period lymphofluoroscopy was performed on both the affected and unaffected hindlimb. Cardiogreen dye (Sigma—Aldrich) was diluted at 1 mg/mL in sterile water, and 5 μ L of this solution were injected intradermally in the dorsum of the paw in anaesthetised rats. Physiological lymphatic drainage of the injected dye was monitored with a PDE Near Infrared Fluorescence Imager (Hamamatsu Photonics, Shizuoka, Japan). The anatomical level reached by the dye was marked on the skin every 5 min, for up to 15 min. Lymphatic drainage speed was calculated by measuring the distance between the injection spot and the skin marks divided by the time interval. MLD, using fill-in and flush manoeuvres,²² was performed in the LE limb 15 min following dye injection.

Drainage device implantation and activation

Eight to ten weeks after irradiation of the hindlimb a drug delivery pump (Ithetis pump; Antlia SA, Lausanne, Switzerland), modified to work in aspiration mode, was implanted in a subcutaneous pocket created in the back of the rat, with the inlet tubing positioned in the subcutaneous tissue in the left hindlimb (lymphoedematous tissue), and the outlet tubing placed in the subcutaneous space close to the pump (Fig. 1). Rats were anaesthetised, and a 2–3 cm incision was made in the back skin. A subcutaneous pocket was created with surgical scissors and a tunnel between the cut in the back and the hindlimb was created with a Kel-F hub 12 G needle, 152 mm long (Hamilton Bonaduz AG, Bonaduz, Switzerland). The inlet tubing was inserted in the inner lumen of the needle and the needle was removed. The pump and outlet tubing were placed in a subcutaneous pocket created in the rat's back. The wound was closed with resorbable sutures and the pump was activated in order to drain 3 μ L/h. Rats were monitored for 5 weeks after implantation of the device. The difference between the volume of the healthy limb



and the lymphoedematous limb was recorded (interlimb difference). Values were normalised to the interlimb difference right before implant. Sham surgery was performed on a second group of rats.

Statistical analysis

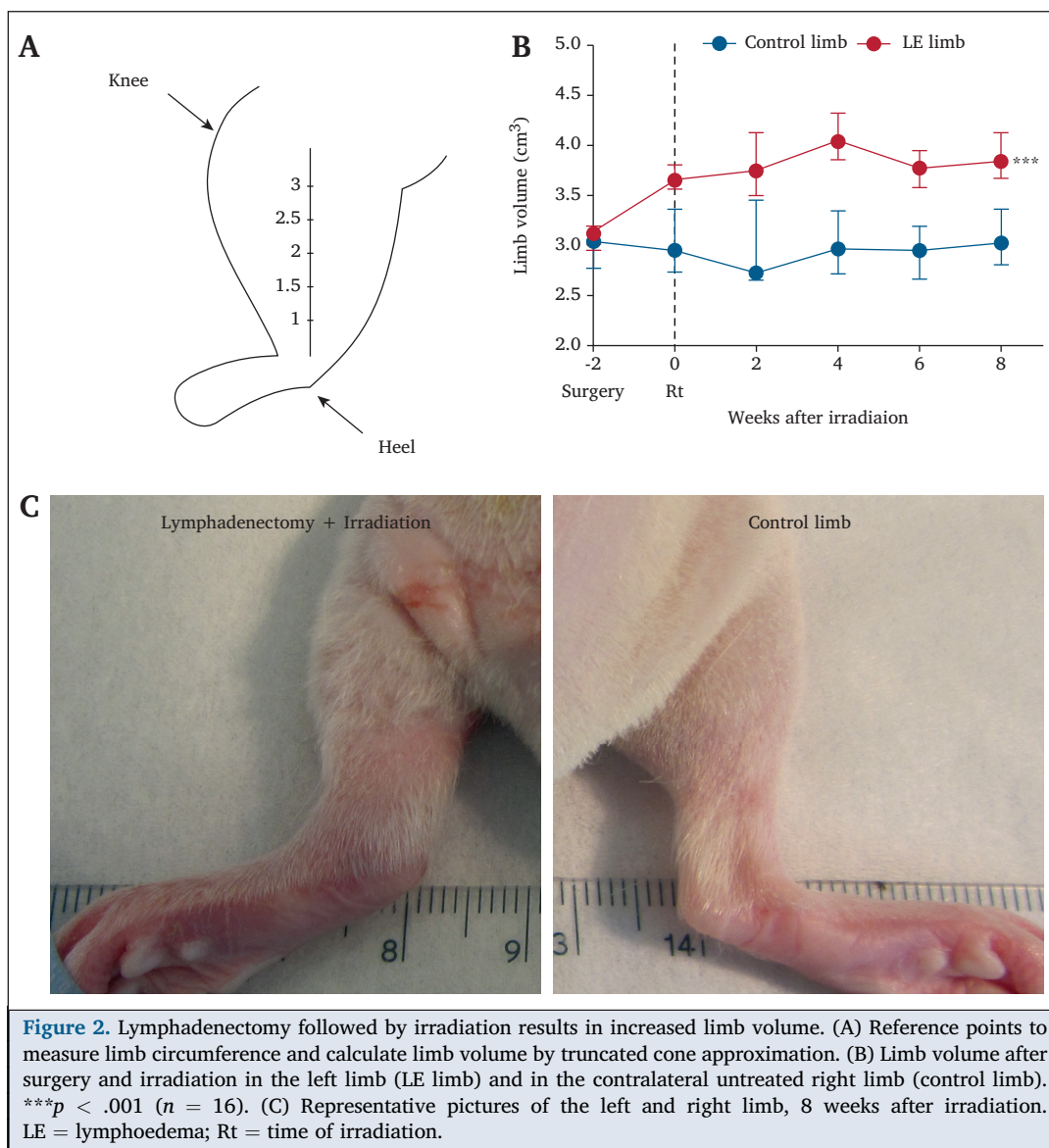
All data shown are expressed as median (interquartile range), unless stated differently in the result section and in the figure legends. Comparisons between the left hindlimb and the right hindlimb, used as internal control, were done by two tailed Wilcoxon signed rank test. Comparison between sham surgery and pump group was done by two tailed Mann–Whitney test. p Values $< .05$ were considered statistically significant.

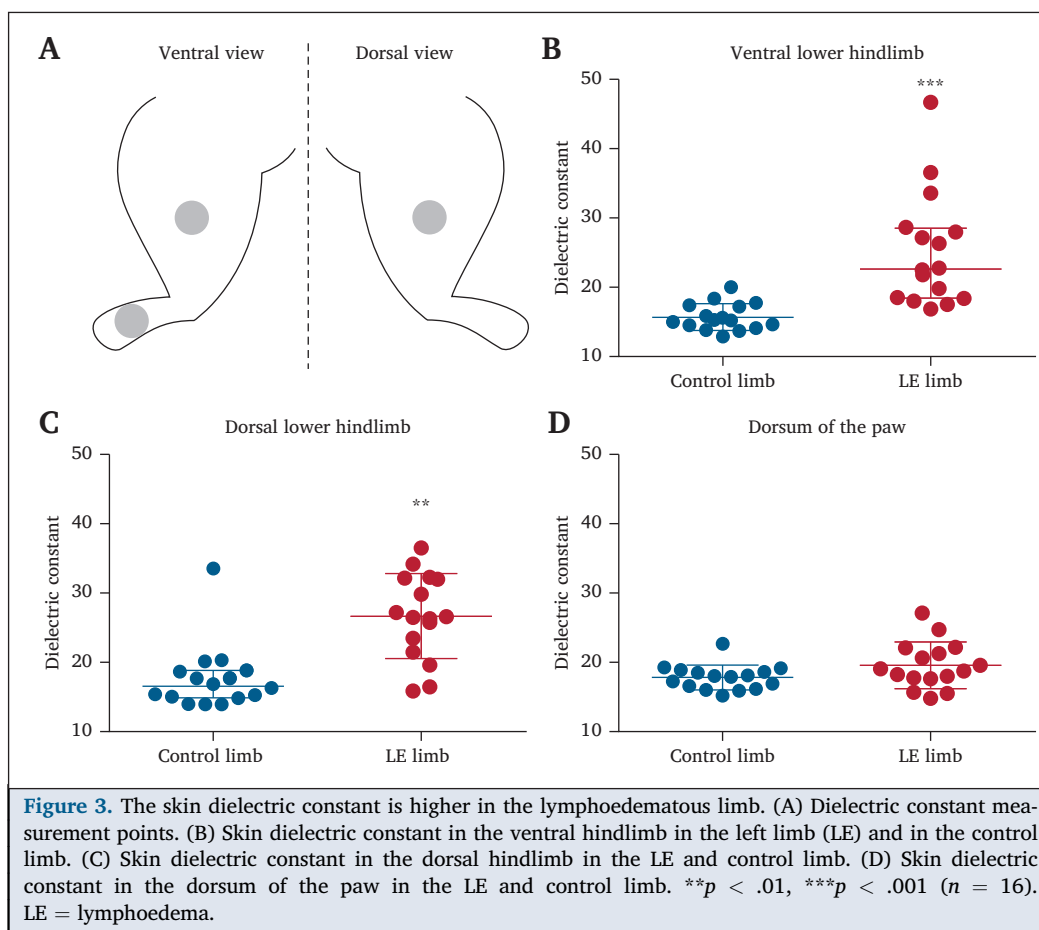
RESULTS

Efficacy of lymphadenectomy/irradiation

Lymph node removal and irradiation caused the formation of a stable oedema, as quantified by a statistically significant increase in hindlimb volume compared with the contralateral side ($3.85 [0.38] \text{ cm}^3$ vs. $3.03 [0.43] \text{ cm}^3$ eight weeks after irradiation [$p = .001$, $n = 16$]; Fig. 2A and B). The lymphoedematous limb was characterised by non-pitting oedema corresponding to the ankle joint and by skin folds similar to the ones observed in patients with LE (Fig. 2C).

Eight weeks after irradiation, the skin dielectric constant was significantly elevated in the oedematous hindlimb, on both the ventral and dorsal side (ventral side: $22.7 [9.7]$ LE





vs. 15.2 [2.9] control [$p = .001$]; dorsal side: 26.6 [9.1] LE vs. 16.5 [3.7] control [$p = .002$]; Fig. 3A–C) but not on the dorsum of the paw (18.9 [3.8] LE vs. 18.0 [2.3] control [$p = .093$]; Fig. 3D).

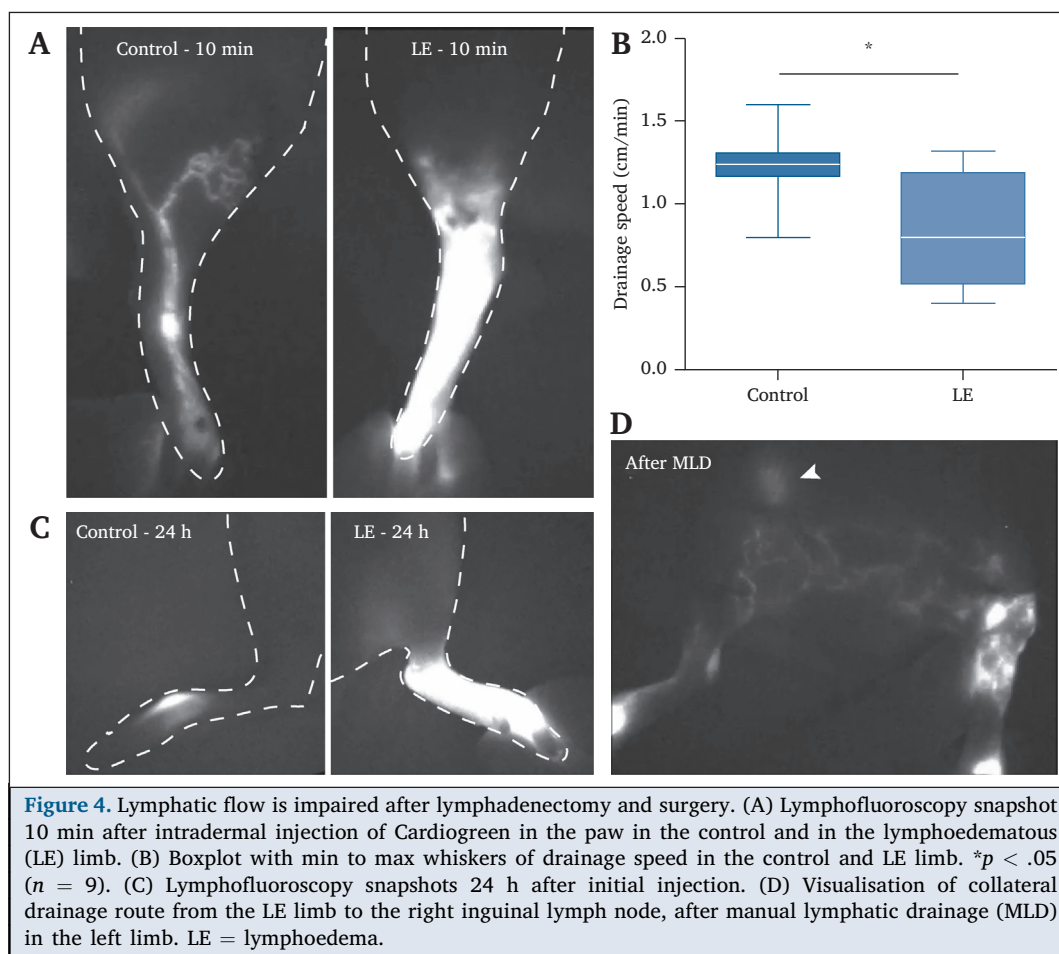
Lymphatic flow

Lymphofluoroscopy was performed to assess lymphatic drainage. Lymphatic vessels were clearly identified in the healthy limb 10 min after injection of the fluorescent tracer. Conversely, in the lymphoedematous limb the injected dye mainly diffused, and no clear routes of drainage were identified (Fig. 4A). Drainage speed was significantly reduced in the oedematous limb compared with the untreated control (Fig. 4B). To confirm impaired drainage capacity in the LE limb, imaging of the injection site was performed 24 h after injection, showing almost complete drainage of the dye in the healthy limb and stagnation of fluid in the LE limb (Fig. 4C). In one case the formation of collateral drainage routes following MLD was observed, connecting the left limb with the right inguinal lymph node (Fig. 4D). These collateral routes were, however, insufficient to sustain

proper lymphatic flow as they could only be visualised following MLD.

Continuous artificial drainage results in hindlimb volume reduction

Five weeks following device implant the interlimb volume difference was reduced by $51 \pm 18\%$ (Fig. 5A [$p = .009$ at week 5]), corresponding to a mean $\pm$ SD interlimb volume reduction of $-0.60 \text{ cm}^3 \pm 0.70$ in the pump group, versus a mean $\pm$ SD interlimb volume increase of $+0.41 \text{ cm}^3 \pm 0.57$ in the sham group (Fig. S2; see Supplementary Material). In four cases the battery lasted 2 weeks after implant, whereas in three cases the battery lasted for 5 weeks. In one case, 1 week after implantation, kinking of the inlet tubing was observed. At week 3 after implant the rat underwent surgery to readjust the tubing position. During the kinking period, while drainage was impaired, a 97% volume increase was observed versus the volume one week post-implant. Following repositioning and re-establishment of correct pump functioning, 2 weeks later, a 53% excess volume reduction was observed (Fig. 5B). No significant



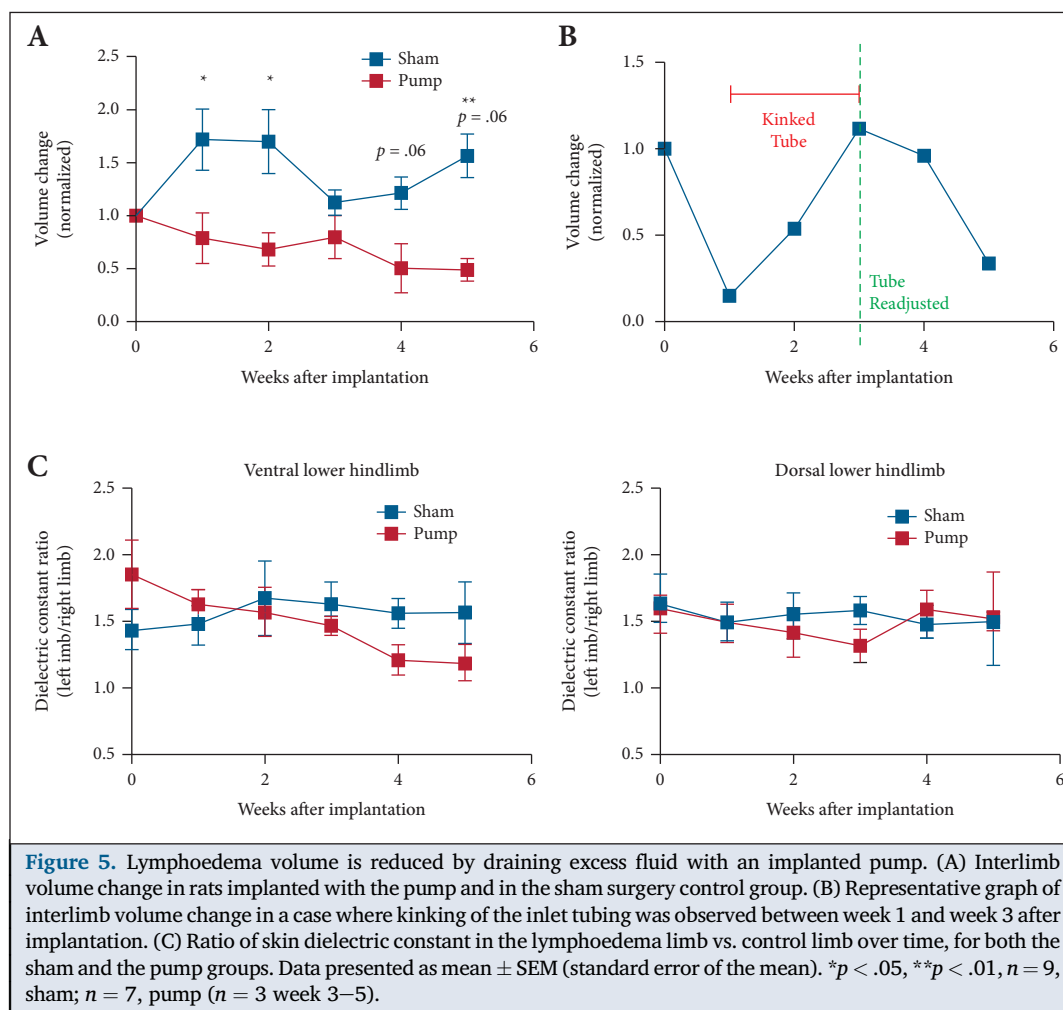
differences in dielectric constant ratio (LE limb/healthy limb) between treated (device) and sham group were observed (Fig. 5C).

DISCUSSION

These results show for the first time, the feasibility of significant LE volume reduction via a subcutaneously implanted device composed of fenestrated tubing equipped with a miniaturised pump. To the best of the authors' knowledge, this is the first time this approach has been investigated. Results were obtained in a chronic rat hindlimb LE model. The model used follows those described previously, adding further knowledge to the characterisation of LE.^{19–21} Adapted to the rat model was the measurement of the dielectric constant (indirect measure of water content), which showed a significant increase in the LE limb. Along the same lines, lymphofluorescence imaging was adapted to the rat to visualise and assess impaired lymphatic drainage.

The rat hindlimb model closely mimics the pathophysiological and anatomical aspects observed in chronic LE

patients, outperforming the rabbit, canine, sheep, and porcine models that either require highly specialised surgical skills, have low reliability, or result only in acute lymphatic damage.^{18,23–25} Minor limitations remain, mainly linked to the size of the animal: lymph flow rates are different between rats and human. Moreover, the model requires irradiation to trigger LE formation, with consequent temporary skin injury and inflammation, and the risk of radiation recall effect as described in patients.²⁶ Nevertheless, despite these limitations, the rat LE hindlimb model proved to be a useful and simple tool to test the feasibility of an innovative approach to LE treatment. It has been shown that continuous drainage of excess fluids from the oedematous limb results in significant LE volume reduction compared with the sham-operated animals. Moreover, it was noticed that interruption of artificial drainage, even for a brief time, is associated with regaining limb volume. The excess volume significantly decreased following device reactivation, strongly suggesting a direct link between artificial drainage and limb volume. Thus, this study shows for the first time the feasibility of treating chronic LE with an



implantable device made of a silicone catheter connected to an active pump.

The internal drainage was performed over a time-frame suitable for observing the dynamics of volume changes in the rat limb, compatible with the battery life of the implantable pump. The pump used for the study was used to obtain proof of concept, and the battery performance observed was not optimal. For clinical translatability of the current approach, a system to ensure proper power supply throughout the lifetime of the device would need to be designed. One approach could be to find a technological solution to completely avoid battery implantation, for example by placing the battery in a wearable device that is magnetically coupled with the implantable pump. No differences were found in the skin dielectric constant after pump activation. This observation could be explained by the fact that the moisture meter probe used for the study (probe S) is designed to measure the dielectric constant of the dermis, whereas the tubing connected to the

pump is placed in the subcutaneous space. The limb volume is affected by the subcutaneous drainage, but the superficial dermis water content is not.

These findings are in line with previous reports that have proposed the use of silicone catheters implanted subcutaneously for the treatment of LE: accumulated interstitial fluid was forced into subcutaneously implanted hollow tubes by mean of external compression with intermittent pneumatic compression pumps.^{11,12} Interestingly, results showed reduction of limb circumference, enhanced drainage, no cellular infiltrates, and no formation of fibrotic tissue around the tubes, both in upper and lower limb LE. Nevertheless, patients still needed to use external compression therapy on a regular basis. Of great interest, the advantage with the system proposed here would be the elimination of the need for external compression: the internal drainage is driven by the implanted pump.

Compared with existing surgical techniques for the treatment of LE, the approach proposed here presents

several advantages. Firstly, the device could be implanted by any surgeon, without the need for the highly specialised skills and the expensive equipment required for microsurgery. Secondly, the surgery would not be limited to patients with functional lymphatics,²⁷ but it could potentially be extended to LE cases where lymphatics are more severely affected. The drainage catheter would work as an artificial vessel, substituting the role of the malfunctioning or completely non-functional lymphatics.

In conclusion, the data presented here validate the rat hindlimb model as an excellent model of chronic LE. Of great importance, for the first time the therapeutic efficacy of the use of an implanted system to reduce LE volume by continuously draining excess fluids from the oedematous area is provided, opening the way to further clinical investigation.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejvs.2018.04.014>.

CONFLICTS OF INTEREST

V.T. and M.P. are founders of Lymphatica Medtech SA. N.S. is founder and director of Antlia SA.

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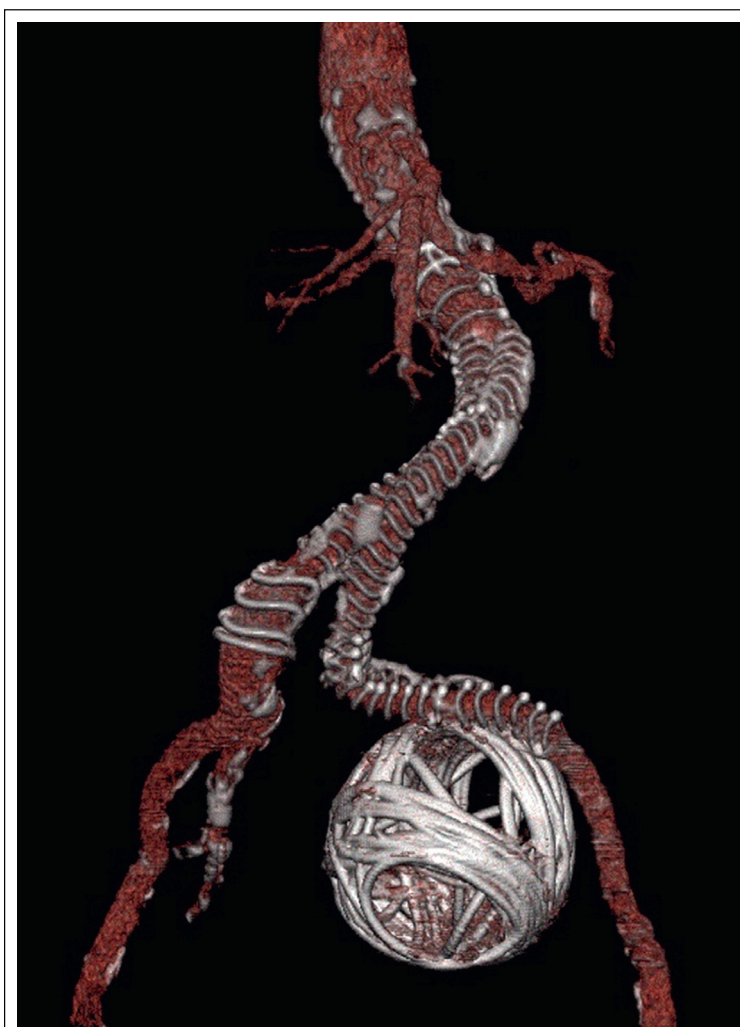
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COUP D'OEIL

A Roll for Guidewires in an Internal Iliac Artery Aneurysm

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An 80 year old man underwent endovascular aneurysm repair of a 50 mm asymptomatic abdominal aortic aneurysm associated with a 73 mm asymptomatic left internal iliac artery aneurysm (LIIAA) with a bifurcated endograft (Anaconda Vascutek; Terumo, Inchinnan, UK). The LIIAA was embolised with 15 hydrophilic floppy guidewires (0.035" Glidewire 180 cm; Terumo). This is not a standard approach in the authors' centre, but was considered in this case as it was effective in providing long wire lengths, and thus the necessary coiling volume, and was also cheaper (€37/wire). This image represents the good treatment result on the two year computed tomography angiogram.

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