Eur J Vasc Endovasc Surg (2019) 57, 859–867

Experimental Drainage Device to Reduce Lymphoedema in a Rat Model

Valentina Triacca [a,1], Marco Pisano [a,1], Claudia Lessert [a], Benoit Petit [b], Karima Bouzourene [a], Aimable Nahimana [c], Marie-Catherine Vozenin [b], Nikolaos Stergiopulos [d], Melody A. Swartz [e], Lucia Mazzolai [a,*]

[a] Angiology Division/Lausanne University Hospital (CHUV), Chemin de Mont Paisible 18, Lausanne, CH 1011, Switzerland
[b] Department of Radiation Oncology/DO/CHUV, Rue du Bugnon 46, Lausanne, CH 1011, Switzerland
[c] Central Laboratory of Hematology/CHUV, Rue du Bugnon 46, Lausanne, CH 1011, Switzerland
[d] Laboratory of Haemodynamics and Cardiovascular Technology, Institute of Bioengineering, Swiss Federal Institute of Technology (EPFL), Station 9, Lausanne, CH 1015, Switzerland
[e] Institute for Molecular Engineering, University of Chicago, 5747 S. Ellis Ave, Chicago, IL 60637, USA

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) cm^3 versus 3.03 (0.43) cm^3 for volume ($n = 16$, $p = .001$) and 26.6 (9.1) versus 16.6 (3.7) cm^3 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
Article history: Received 15 February 2018, Accepted 22 April 2018, Available online 25 May 2019
© 2018 The Authors. Published by Elsevier B.V. on behalf of European Society for Vascular Surgery. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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

[1] V. Triacca and M. Pisano contributed equally to this work.

* Corresponding author. Angiology Division/CHUV, Chemin de Mont Paisible 18, Lausanne, CH 1011, Switzerland.
E-mail address: lucia.mazzolai@chuv.ch (Lucia Mazzolai).

1078-5884/© 2018 The Authors. Published by Elsevier B.V. on behalf of European Society for Vascular Surgery. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
https://doi.org/10.1016/j.ejvs.2018.04.014

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 µL 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 maneouvres,[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 µL/h. Rats were monitored for 5 weeks after implantation of the device. The difference between the volume of the healthy limb

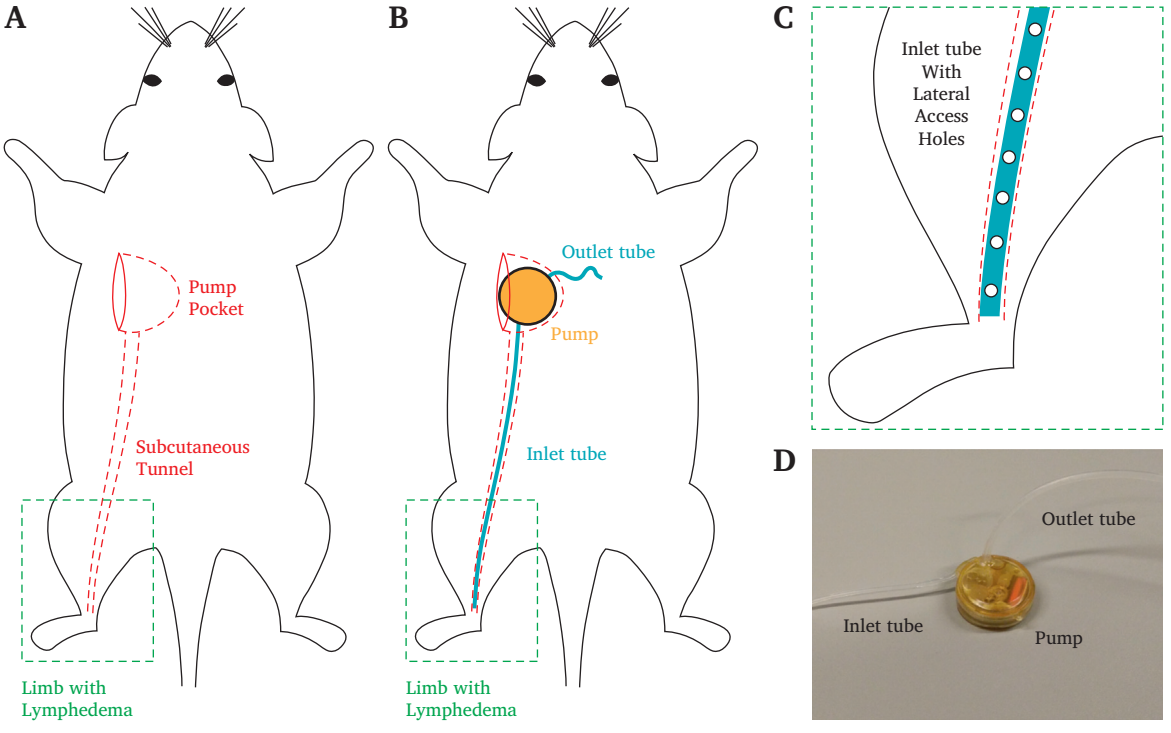


Figure 1. Subcutaneous implantation of a drainage pump connected to a silicone tube. (A) Schematic drawing of the implant surgery. (B) Schematic drawing of the inlet tube, the pump, and the outlet tube in the subcutaneous pocket created during the surgical procedure. (C) Close up of the lymphoedematous area showing the lateral access holes in the inlet tube. (D) Drug delivery device modified to work in aspiration mode (pump [Antlia SA, Lausanne, Switzerland], diameter = 21 mm, thickness = 7 mm).

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] cm^3 vs. 3.03 [0.43] 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

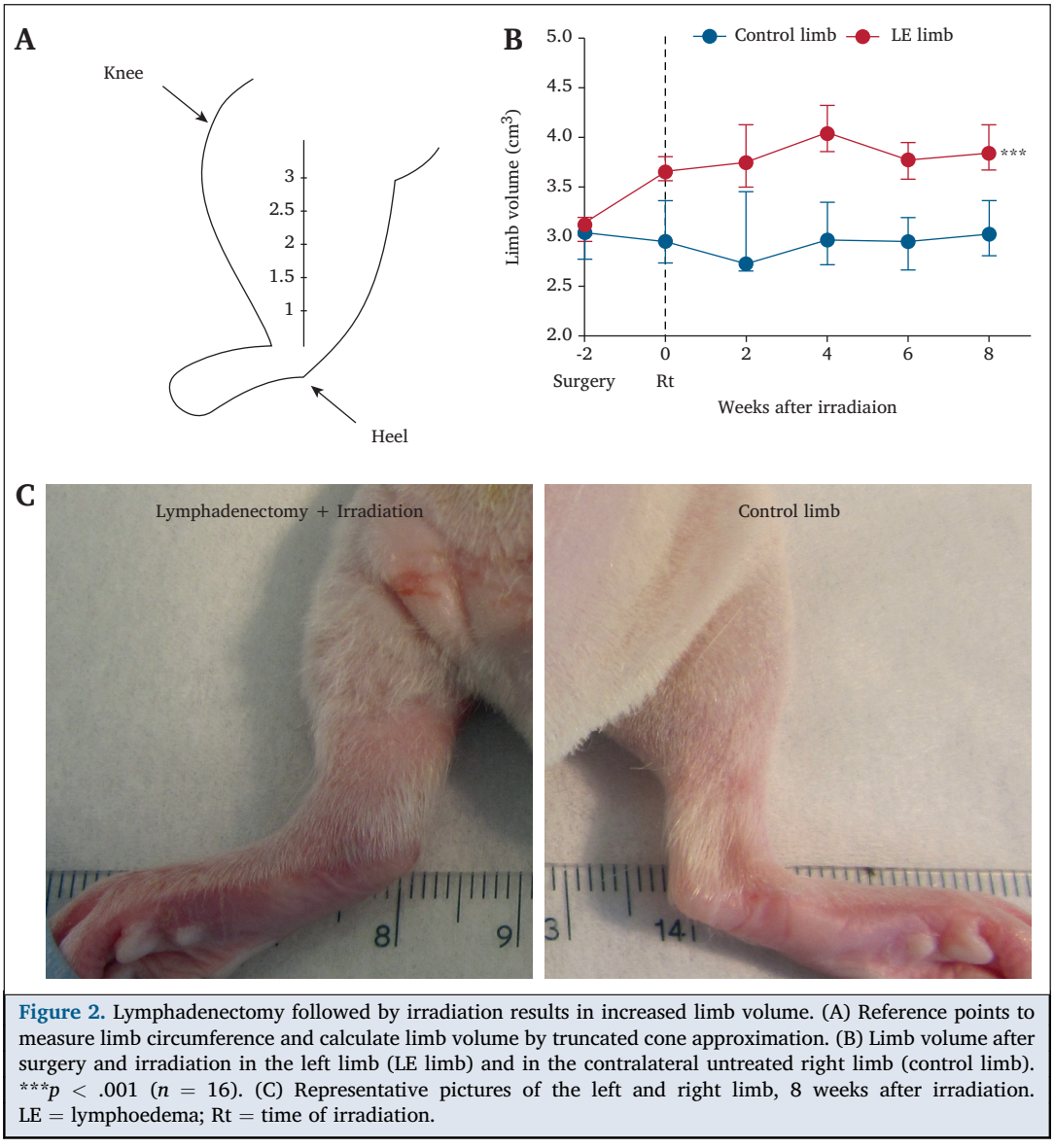


Figure 2. Lymphadenectomy followed by irradiation results in increased limb volume. (A) Reference points to measure limb circumference and calculate limb volume by truncated cone approximation. (B) Limb volume after surgery and irradiation in the left limb (LE limb) and in the contralateral untreated right limb (control limb). ***$p < .001$ ($n = 16$). (C) Representative pictures of the left and right limb, 8 weeks after irradiation. LE = lymphoedema; Rt = time of irradiation.

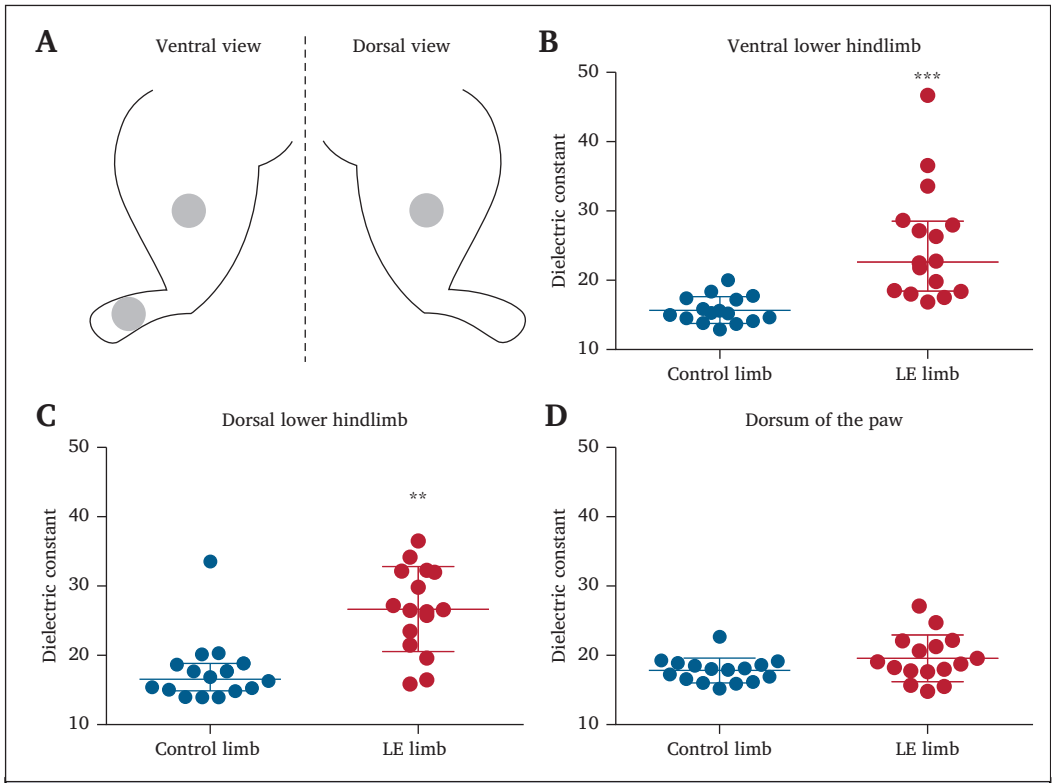


Figure 3. The skin dielectric constant is higher in the lymphoedematous limb. (A) Dielectric constant measurement points. (B) Skin dielectric constant in the ventral hindlimb in the left limb (LE) and in the control limb. (C) Skin dielectric constant in the dorsal hindlimb in the LE and control limb. (D) Skin dielectric constant in the dorsum of the paw in the LE and control limb. $^{**}p < .01$, $^{***}p < .001$ ($n = 16$). LE = lymphoedema.

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 ± 18% (Fig. 5A [$p = .009$ at week 5]), corresponding to a mean ± SD interlimb volume reduction of −0.60 cm^3 ± 0.70 in the pump group, versus a mean ± SD interlimb volume increase of +0.41 cm^3 ± 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

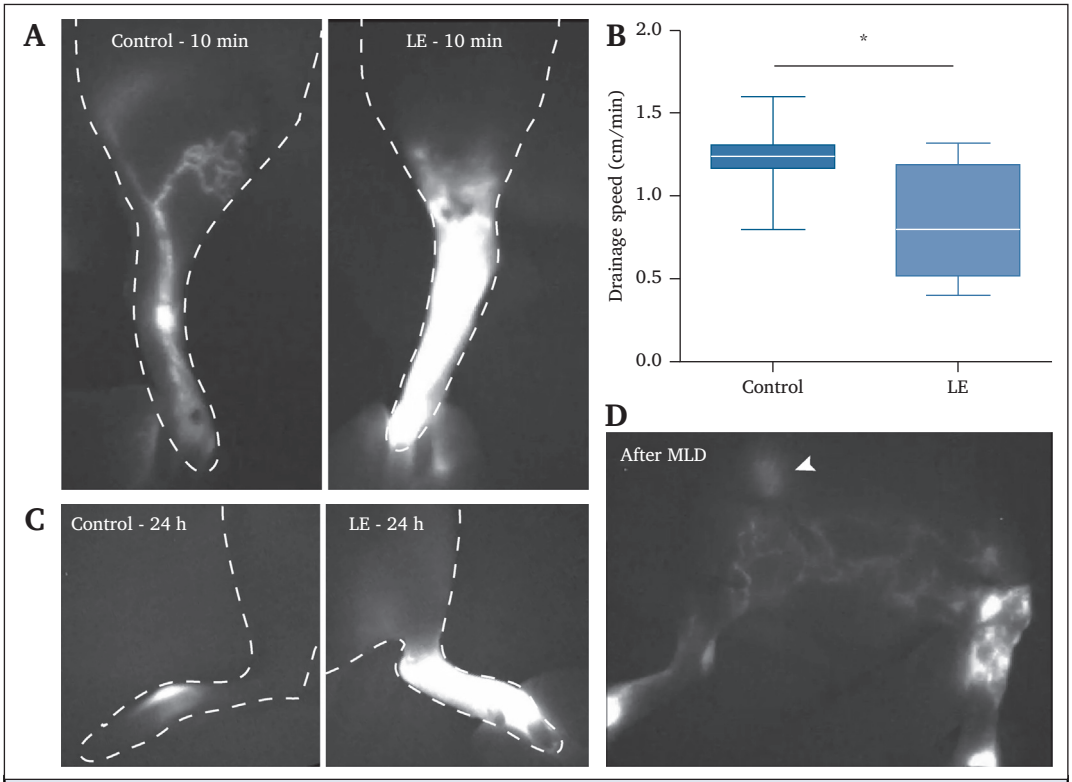


Figure 4. Lymphatic flow is impaired after lymphadenectomy and surgery. (A) Lymphofluoroscopy snapshot 10 min after intradermal injection of Cardiogreen in the paw in the control and in the lymphoedematous (LE) limb. (B) Boxplot with min to max whiskers of drainage speed in the control and LE limb. *$p < .05$ ($n = 9$). (C) Lymphofluoroscopy snapshots 24 h after initial injection. (D) Visualisation of collateral drainage route from the LE limb to the right inguinal lymph node, after manual lymphatic drainage (MLD) in the left limb. LE = lymphoedema.

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, lymphofluoroscopy 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

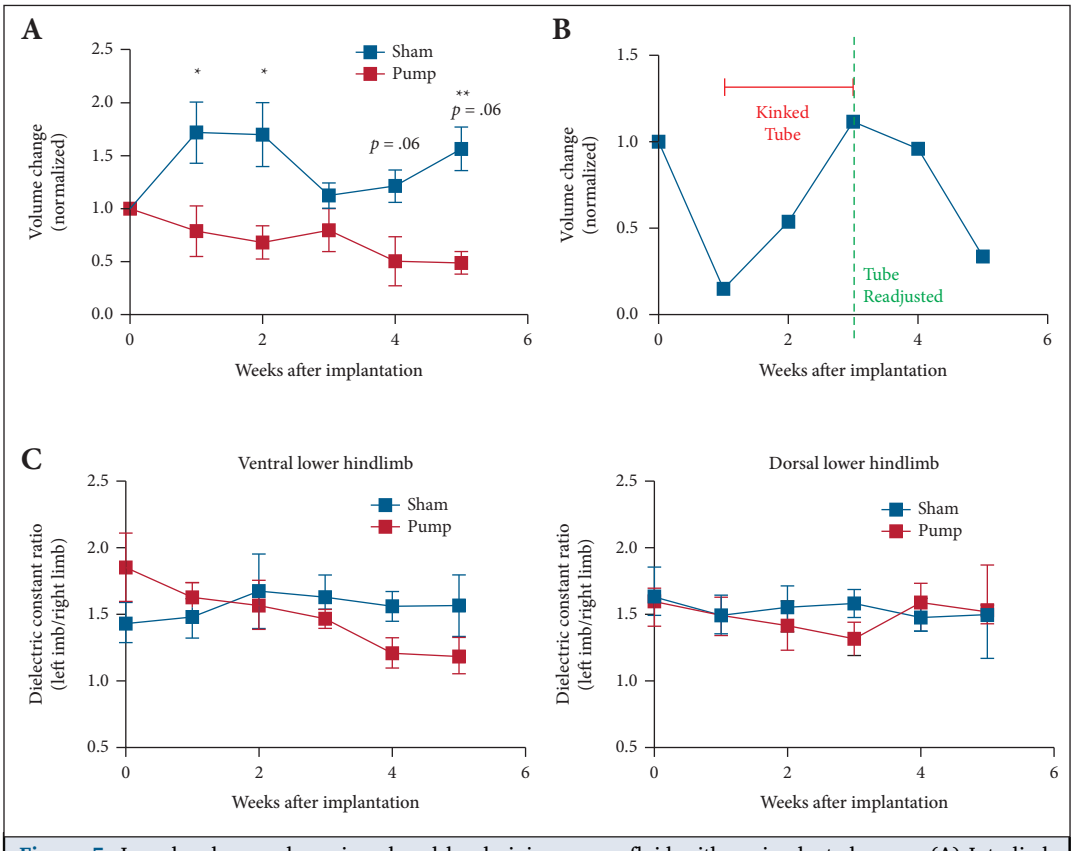


Figure 5. Lymphoedema volume is reduced by draining excess fluid with an implanted pump. (A) Interlimb volume change in rats implanted with the pump and in the sham surgery control group. (B) Representative graph of interlimb volume change in a case where kinking of the inlet tubing was observed between week 1 and week 3 after implantation. (C) Ratio of skin dielectric constant in the lymphoedema limb vs. control limb over time, for both the sham and the pump groups. Data presented as mean ± SEM (standard error of the mean). $*p < .05$, $**p < .01$, $n = 9$, sham; $n = 7$, pump ($n = 3$ week 3–5).

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.

ACKNOWLEDGMENTS

The authors are grateful to Dr Maxime Pellegrin, Dr Kalitha Pinnagoda, Melanie Sipion, Sébastien Pittet, and Michel Bachmann.

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.

FUNDING

Swiss Commission for Technology and Innovation [18021.1 PFLS-LS to L.M.]; Fondation pour l'Innovation Technologique grant to M.P; Subside Emma Muschamp to V.T.

REFERENCES

1 Ribeiro Pereira ACP, Koifman RJ, Bergmann A. Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up. *Breast* 2017;**36**:67–73.
2 Nguyen TT, Hoskin TL, Habermann EB, Cheville AL, Boughey JC. Breast cancer-related lymphedema risk is related to multidisciplinary treatment and not surgery alone: results from a large cohort study. *Ann Surg Oncol* 2017;**24**:2972–80.
3 Hayes SC, Janda M, Ward LC, Reul-Hirche H, Steele ML, Carter J, et al. Lymphedema following gynecological cancer: results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors. *Gynecol Oncol* 2017;**146**:623–9.
4 Moody JA, Botham SJ, Dahill KE, Wallace DL, Hardwicke JT. Complications following completion lymphadenectomy versus therapeutic lymphadenectomy for melanoma – a systematic review of the literature. *Eur J Surg Oncol* 2017;**43**:1760–7.
5 Lee BB, Andrade M, Antignani PL, Boccardo F, Bunke N, Campisi C, et al. Diagnosis and treatment of primary lymphedema. Consensus document of the International Union of Phlebology (IUP)-2013. *Int Angiol* 2013;**32**:541–74.
6 Campisi C, Eretta C, Pertile D, Da Rin E, Maccio A, Campisi M, et al. Microsurgery for treatment of peripheral lymphedema: long-term outcome and future perspectives. *Microsurgery* 2007;**27**:333–8.
7 Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S. Long-term follow-up after lymphaticovenular anastomosis for lymphedema in the leg. *J Reconstr Microsurg* 2003;**19**:209–15.
8 Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. *Plast Reconstr Surg* 2010;**126**:752–8.
9 Batista BN, Germain M, Faria JCM, Becker C. Lymph node flap transfer for patients with secondary lower limb lymphedema. *Microsurgery* 2017;**37**:29–33.
10 Scaglioni MF, Arvanitakis M, Chen YC, Giovanoli P, Chia-Shen Yang J, Chang EI. Comprehensive review of vascularized lymph node transfers for lymphedema: outcomes and complications. *Microsurgery* 2018;**38**:222–9.
11 Olszewski WL, Zaleska M. A novel method of edema fluid drainage in obstructive lymphedema of limbs by implantation of hydrophobic silicone tubes. *J Vasc Surg Venous Lymphat Disord* 2015;**3**:401–8.
12 Olszewski WL, Zaleska M. Treatment of postmastectomy lymphedema by bypassing the armpit with implanted silicone tubings. *Int Angiol* 2017;**36**:50–8.
13 McWayne J, Heiney SP. Psychologic and social sequelae of secondary lymphedema: a review. *Cancer* 2005;**104**:457–66.
14 Lanza M, Bergmann A, Ferreira MG, de Aguiar SS, Dias Rde A, Abrahao Kde S, et al. Quality of life and volume reduction in women with secondary lymphoedema related to breast cancer. *Int J Breast Cancer* 2015;**2015**:586827.
15 Alcorso J, Sherman KA. Factors associated with psychological distress in women with breast cancer-related lymphoedema. *Psychooncology* 2016;**25**:865–72.
16 Frueh FS, Gousopoulos E, Rezaeian F, Menger MD, Lindenblatt N, Giovanoli P. Animal models in surgical lymphedema research – a systematic review. *J Surg Res* 2015;**200**:208–20.
17 Hadamitzky C, Pabst R. Acquired lymphedema: an urgent need for adequate animal models. *Cancer Res* 2008;**68**:343–5.
18 Lahteenvuo M, Honkonen K, Tervala T, Tammela T, Suominen E, Lahteenvuo J, et al. Growth factor therapy and autologous lymph node transfer in lymphedema. *Circulation* 2011;**123**:613–20.
19 Yang CY, Nguyen DH, Wu CW, Fang YHD, Chao KT, Patel KM, et al. Developing a lower limb lymphedema animal model with combined lymphadenectomy and low-dose radiation. *Plast Reconstr Surg Glob Open* 2014;**7**:e121.
20 Lee-Donaldson L, Witte MH, Bernas M, Witte CL, Way D, Stea B. Refinement of a rodent model of peripheral lymphedema. *Lymphology* 1999;**32**:111–7.
21 Kanter MA, Slavin SA, Kaplan W. An experimental model for chronic lymphedema. *Plast Reconstr Surg* 1990;**85**:573–80.
22 Belgrado JP, Vandermeeren L, Vankerckhove S, Valsamis JB, Malloizel-Delaunay J, Moraine JJ, et al. Near-infrared fluorescence lymphatic imaging to reconsider occlusion pressure of superficial lymphatic collectors in upper extremities of healthy volunteers. *Lymphat Res Biol* 2016;**14**:70–7.
23 Chen HC, Pribaz JJ, O'Brien BM, Knight KR, Morrison WA. Creation of distal canine limb lymphedema. *Plast Reconstr Surg* 1989;**83**:1022–6.
24 Tobbia D, Semple J, Baker A, Dumont D, Semple A, Johnston M. Lymphedema development and lymphatic function following lymph node excision in sheep. *J Vasc Res* 2009;**46**:426–34.
25 Szuba A, Skobe M, Karkkainen MJ, Shin WS, Beynet DP, Rockson NB, et al. Therapeutic lymphangiogenesis with human recombinant VEGF-C. *FASEB J* 2002;**16**:1985–7.

26 Azria D, Magne N, Zouhair A, Castadot P, Culine S, Ychou M, et al. Radiation recall: a well recognized but neglected phenomenon. *Cancer Treat Rev* 2005;**31**:555–70.

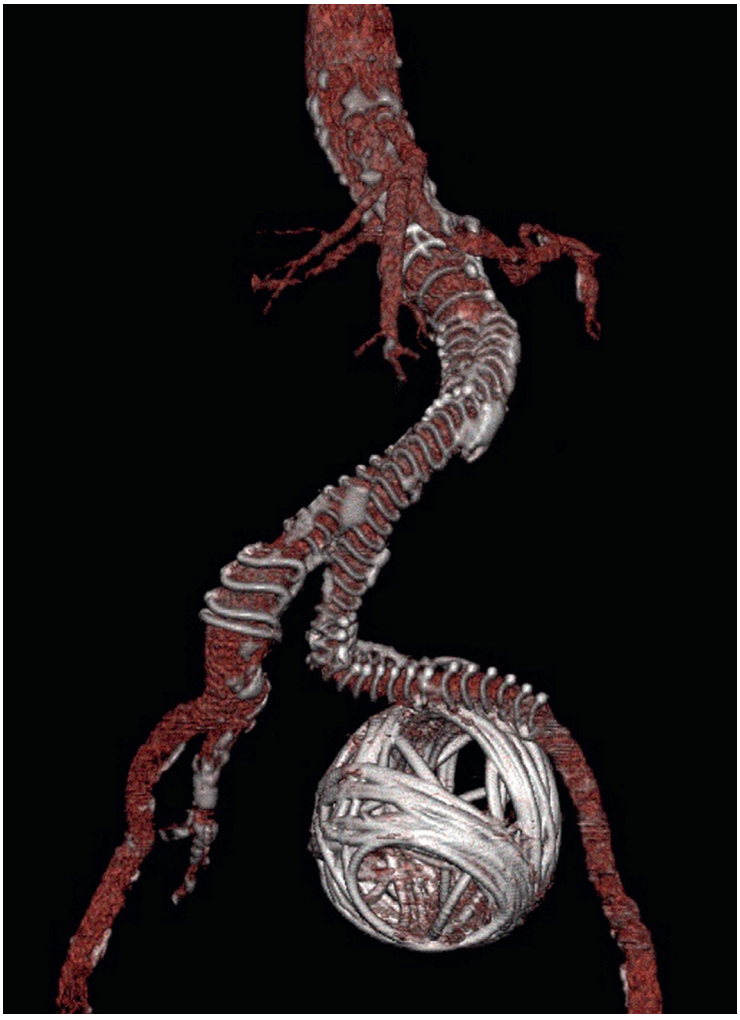
27 Olszewski WL. Lymphovenous microsurgical shunts in treatment of lymphedema of lower limbs: a 45-year experience of one surgeon/one center. *Eur J Vasc Endovasc Surg* 2013;**45**:282–90.

Eur J Vasc Endovasc Surg (2019) 57, 867

COUP D'OEIL

A Roll for Guidewires in an Internal Iliac Artery Aneurysm

Mara Fanelli *, **Tiziano Tecchio**
Vascular Surgery, Department of Medicine and Surgery, University of Parma, Parma, Italy



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.

* Corresponding author. Vascular Surgery, Department of Medicine and Surgery, University of Parma, 14 via Gramsci, 43126 Parma, Italy.
E-mail address: mara.fanelli@libero.it (Mara Fanelli).
1078-5884/© 2019 European Society for Vascular Surgery. Published by Elsevier B.V. All rights reserved.
https://doi.org/10.1016/j.ejvs.2019.02.013