Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Research review

Animal models in surgical lymphedema research—a systematic review

Florian S. Frueh, MD,[a] *Epameinondas Gousopoulos, MD, MSc,*[b] *Farid Rezaeian, MD,*[a] *Michael D. Menger, MD,*[c] *Nicole Lindenblatt, MD,*[a,*,1] *and Pietro Giovanoli, MD*[a,1]

[a] *Division of Plastic Surgery and Hand Surgery, University Hospital Zurich, Zurich, Switzerland*
[b] *Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology, ETH Zurich, Zurich, Switzerland*
[c] *Institute for Clinical and Experimental Surgery, University of Saarland, Homburg/Saar, Germany*

ARTICLE INFO

Article history:
Received 23 April 2015
Received in revised form
24 June 2015
Accepted 2 July 2015
Available online 9 July 2015

Keywords:
Animal model
Lymphatic system
Lymphedema
Lymph node transplantation

ABSTRACT

Background: Chronic secondary lymphedema is a well-known complication in oncologic surgery. Autologous lymph node transplantation, lymphovenous anastomosis, and other lymphatic surgeries have been developed in the last decades with rising clinical application. Animal models to explore the pathophysiology of lymphedema and microsurgical interventions have reached great popularity, although the induction of stable lymphedema in animals is still challenging. The aim of this review was to systematically assess lymphedema animal models and their potential use to study surgical interventions.

Materials and methods: A systematic review according to the PRISMA guidelines was performed without time or language restriction. Studies describing new or partially new models were included in chronological order. Models for primary and secondary lymphedema were assessed, and their potential for surgical procedures was evaluated.

Results: The systematic search yielded 8590 discrete articles. Of 180 articles included on basis of title, 84 were excluded after abstract review. Ninety-six were included in the final analysis with 24 key articles.

Conclusions: No animal model is perfect, and many models show spontaneous lymphedema resolution. The rodent limb appears to be the most eligible animal model for experimental reconstruction of the lymphatic function as it is well accessible for vascularized tissue transfer. There is a need for standardized parameters in experimental lymphedema quantification. Also, more permanent models to study the effect of free vascularized lymph node transfer are needed.

* *Corresponding author*. Division of Plastic Surgery and Hand Surgery, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. Tel.: +41 44 255 11 11; fax: +41 44 255 89 77.
E-mail address: niclindenblatt@hotmail.com (N. Lindenblatt).
[1] These authors contributed equally to this work.
0022-4804/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jss.2015.07.005

1. Introduction

Beside to the blood vasculature, the lymphatic system significantly contributes to the regulation of vital functions in the human body, including the control of tissue pressure, immune surveillance, and intestinal dietary fat absorption [1]. It consists of lymphatic capillaries, precollecting vessels, and collecting lymphatic trunks, which form a three-dimensional network with interposed lymph nodes. The lymph nodes represent the "immunologic center" of the lymphatic network and are essential for the initiation of immune responses. Furthermore, the lymphatic system is involved in several pathologic processes such as lymphedema, cancer dissemination, and inflammatory disorders [1,2]. Failure of the lymphatic system to efficiently drain the extravasated fluid leads to accumulation of lymph in the interstitial tissue, causing lymphedema. Its chronic form is characterized by swelling, tissue fibrosis, adipose tissue accumulation, and immune cell infiltration.

Lymphedema can be classified based on its cause. Primary lymphedema, further classified by the age of onset as hereditary, praecox, or tarda, is a rare disease with an estimated prevalence rate of 1.15 per 100,000 subjects in North America [3]. It originates from causal mutations affecting lymphatic development and usually involves the lower extremities of female patients. Milroy syndrome (Vascular endothelial growth factor receptor-3 [VEGFR-3] encoding gene), Meige syndrome (mutation unknown), lymphedema-distichiasis (FOXC2 on chromosome 16), and yellow nail syndrome are hereditary diseases associated with primary lymphedema [4,5].

In contrast, secondary (acquired) lymphedema represents a common complication after operative procedures in oncologic surgery, such as axillary or inguinal lymph node dissection in the context of breast cancer or melanoma treatment [6]. Up to 30% of women treated for breast cancer and around 20% of patients after inguinal lymph node dissection for melanoma develop lymphedema [7,8]. Although the extent of surgery correlates with the risk of developing permanent lymphedema [9], secondary lymphedema has also been described after sentinel lymph node biopsy [7]. In addition, radiation, infectious diseases (i.e., lymphatic filariasis), or chronic inflammation may also cause secondary lymphedema. According to the 2014 World Health Organization report, (http://www.who.int/mediacentre/factsheets/fs102/en/index.html) over 15 million people are suffering from lymphedema because of lymphatic filariasis, making it the most important etiology of secondary lymphedema in developing countries. However, in industrialized countries, cancer treatment as outlined above is the most frequent cause of secondary lymphedema.

Despite advances in all fields of surgery, physiotherapy (i.e., lymph drainage, compressive bandages) remains the standard symptomatic treatment for both primary and secondary lymphedema. However, as the disease can be caused by surgical intervention, surgical treatment has been discussed over decades. Ablative and invasive surgery are not applied anymore today because of high morbidity and bad cosmetic outcome [10,11]. Since super-microsurgical techniques (i.e., the possibility of lymphatic vessel anastomosis and vascularized lymph node transfer) have become available, lymphovenous anastomosis (LVA), lymphatic vessel transplantation, and autologous lymph node transplantation (ALNT) exhibit encouraging results in reconstructive microsurgery [12,13]. Moreover, the progress in the surgical field coupled with the advances in tissue-engineering render the transplantation of engineered lymph nodes and lymphatic vessels as promising approaches to restore lymphatic function for the treatment of lymphedema [14,15].

Because lymphedema is a complex disease involving a multitude of tissue components, the development of *in vitro* systems to dissect its pathophysiology is difficult. Hence, the use of animal models is indispensable. Various preclinical models, ranging from dogs to rodents, have been developed to investigate the underlying biology of lymphedema and explore therapeutic interventions. In the light of evolving microsurgical procedures to treat lymphedema, there is a lack of evidence for their clinical efficacy, confining surgical management of lymphedema as case series and anecdotal reports [16]. We understand that there is a need for reliable experimental animal models, reproducibly replicating the disease pathophysiology and potential curative treatments to refine these techniques. Therefore, it has been the aim of this review to systematically assess the different lymphedema animal models, analyzing the accessibility for the exploration of surgery-based treatment options.

2. Materials and methods

2.1. *Systematic review*

A review protocol was designed in advance and has been registered on http://www.dcn.ed.ac.uk/camarades//research.html#protocols. We performed a systematic review in accordance to the PRISMA guidelines [17]. Details of the review process are shown in Table 1. In brief, search terms were focused on animal models and lymphedema, excluding clinical trials, reviews, and nonrelated disease models. Each study was verified for the relevance to the topic and from the surgeon's point of view (required microsurgical skills and/or equipment, Table 2).

The systematic search yielded 8590 discrete articles. Of 180 articles included on basis of title, 84 were excluded after abstract review. Ninety-six were included in the final analysis with 24 key articles describing new or partially new models. The detailed selection process is shown in Figure 1.

3. Results

The results have been categorized based on the animal model to enable categorized comparisons. Owing to the heterogeneity of the studies, including the techniques to induce lymphedema, the therapeutic approaches attempted, and the surgical relevance, the results have been organized into table format facilitating visual paralleling.