Intraoperatively Detected But Previously Indocyanine Green-Negative Lymphatic Vessels May Have Misprized Potentials and Should Not Be Neglected in Lymphaticovenous Bypass Surgery

Scaglioni, Mario F ; Uyulmaz, Semra ; Arvanitakis, Michael ; Lineaweaver, William C ; Zhang, Feng

Abstract: INTRODUCTION Identification of patent lymphatic vessels without fibrosis and with high flow is difficult but crucial in the preoperative planning of lymphaticovenous anastomosis (LVA). Lymphatic vessels on the operating field cannot always be visualized preoperatively because of the anatomical and physiological characteristics of lymphedema tissue. The purposes of this study were to demonstrate our clinical experience in identifying indocyanine green (ICG)-negative lymphatics intraoperatively and to emphasize the therapeutic potential of performing anastomoses with ICG-negative lymphatics. METHODS Indocyanine green-positive lymphatic ducts were marked preoperatively in 5 patients with lower extremity lymphedema; moreover, if ICG-negative lymphatics were identified during surgery, they were used for additional LVA thus implementing multiple anastomoses in one surgical setting. RESULTS In total, 33 LVAs were performed in 5 patients with lower extremity lymphedema, of which 11 LVAs were implemented with ICG-negative lymphatics. Immediately after the anastomosis, a strong lymphatic drainage could be appreciated in all cases. Six months postoperatively patients reported a subjective decrease in limb circumference and pressure sensation. CONCLUSIONS We believe that ICG-negative lymphatics found intraoperatively should be evaluated for additional LVAs in order to maximize drainage effect and might provide better outcomes.

DOI: https://doi.org/10.1097/SAP.0000000000001781

Intraoperatively Detected But Previously Indocyanine Green–Negative Lymphatic Vessels May Have Misprized Potentials and Should Not Be Neglected in Lymphaticovenous Bypass Surgery

Mario F. Scaglioni, MD,† Semra Uyulmaz, MD,† Michael Arvanitakis, MD,‡ William C. Lineaweaver, MD, FACS,§ and Feng Zhang, MD§*

Introduction: Identification of patent lymphatic vessels without fibrosis and with high flow is difficult but crucial in the preoperative planning of lymphaticovenous anastomosis (LVA). Lymphatic vessels on the operating field cannot always be visualized preoperatively because of the anatomical and physiological characteristics of lymphedema tissue. The purposes of this study were to demonstrate our clinical experience in identifying indocyanine green (ICG)–negative lymphatics intraoperatively and to emphasize the therapeutic potential of performing anastomoses with ICG-negative lymphatics.

Methods: Indocyanine green–positive lymphatic ducts were marked preoperatively in 5 patients with lower extremity lymphedema; moreover, if ICG-negative lymphatics were identified during surgery, they were used for additional LVA thus implementing multiple anastomoses in one surgical setting.

Results: In total, 33 LVAs were performed in 5 patients with lower extremity lymphedema, of which 11 LVAs were implemented with ICG-negative lymphatics. Immediately after the anastomosis, a strong lymphatic drainage could be appreciated in all cases. Six months postoperatively patients reported a subjective decrease in limb circumference and pressure sensation.

Conclusions: We believe that ICG-negative lymphatics found intraoperatively should be evaluated for additional LVAs in order to maximize drainage effect and might provide better outcomes.

Key Words: ICG, ICG-negative lymphatics, LVA, lymphatic surgery, lymphedema

(*Ann Plast Surg* 2019;83: 69–72)

Lymphaticovenous anastomosis (LVA) has gained worldwide acceptance as a valuable therapy for lymphedema over the last decade. Throughout the preoperative planning of LVA, detection of patent lymphatic vessels without fibrosis and with high flow for anastomosis is crucial but also very difficult. Lymphatic vessels on the operating field cannot always be visualized preoperatively by near-infrared fluorescence imaging using indocyanine green (ICG) because of the anatomical and physiological characteristics of lymphedema tissue. Previously, ICG-negative lymphatics were identified intraoperatively and used to implement multiple anastomoses in 1 surgical setting in order to increase the lymphatic drainage effect. The purposes of this study were to demonstrate our clinical experience in identifying ICG-negative lymphatics intraoperatively and to emphasize the therapeutic potential of performing multiple anastomoses with ICG-negative lymphatics.

PATIENTS AND METHODS

Subjects of this study included 5 patients with lower extremity lymphedema (LEL). They were referred to the Plastic, Reconstructive and Aesthetic Surgery Department of the University Hospital in Zurich between May 2016 and September 2017 with persistent and constant degree of symptoms such as pain, swelling, and recurrent skin infections for a period of 3 months or longer before consultation. All patients had preoperatively undergone at least 1 period of a long-term decongestive therapy, which includes manual lymphatic drainage with meticulous skin and nail care, therapeutic exercise, and limb compression using repetitively applied short-stretch bandages. Vascular ultrasonography was performed to rule out any venous anomaly. Clinical examination, lymphoscintigraphy, and mainly ICG were performed for diagnosis and classification of lymphedema. One patient (case 1) had a lymphedema with International Society of Lymphedema (ISL) Stadium II-III. All other patients (patients 2–5) had a lymphedema with ISL stadium II.

Lymphaticovenous anastomosis surgery was planned under general anesthesia, whenever clinical abnormalities were found in ICG or lymphoscintigraphy, which were consistent with the clinical history and presentation of the patients. Indocyanine green was used as preoperative and intraoperative navigation. Small skin incisions were performed above the previously located lymphatic vessels, which were anastomosed supermicrosurgically to nearby veins whenever possible. Before closure, the surgical site was examined meticulously under the microscope in order to investigate the existence of additional lymphatics. If additional lymphatics were discovered under the microscope, ICG was used to control their ICG negativeness. Whenever this type of lymphatics was identified in the operating field during surgery, additional LVA was performed in standardized manner. Postoperatively, patients were followed up 10 to 14 days, and postoperative limb compression therapy was continued. Patients were seen in the outpatient clinic 3 and 6 months after the intervention.

RESULTS

Multiple LVAs were performed in 5 patients with LEL. The age of patients ranged from 40 to 61 years (mean, 49 years). Four females and 1 male patient were included, of which 3 patients suffered from primary and 2 from secondary lymphedema. Secondary lymphedema had occurred after pelvic cancer surgery in all cases. One patient had undergone additional radiation therapy. Table 1 shows demographic data. Thirty-three LVAs were performed in total. On average, 6.6 LVAs were performed per patient. In all subjects, ICG-negative lymphatics were detected intraoperatively and were used to implement additional anastomoses. Eleven LVAs (33%) were implemented with ICG-negative lymphatics. Table 2 shows the total number of LVAs, if intraoperatively

Received June 30, 2018, and accepted for publication, after revision October 28, 2018.
From the *Department of Hand- and Plastic Surgery, Luzerner Kantonsspital, Lucerne; †Department of Plastic and Hand Surgery, University Hospital Zurich, Zurich; and ‡Kantonssiptal Sant Gallen, Sant Gallen, Switzerland; and §Joseph M. Still Burn and Reconstructive Center, Jackson, MS.

M.F.S. and S.U. should be considered co–first authors.
Conflicts of interest and sources of funding: none declared.
Reprints: Mario F. Scaglioni, MD, Department of Plastic and Hand Surgery, Lucerne Knatonsspital, Spitalstrasse, 6000 Luzern 16 Switzerland. E-mail: Mario.scaglioni@gmail.com.

ISSN: 0148-7043/19/8301–0069
DOI: 10.1097/SAP.0000000000001781

TABLE 1. Patient Characteristics

Case	Age, y	Sex	Type of LEL	Cause of LEL	Body Mass Index, kg/m^2	Total No. LVAs	No. ICG-Positive LVA Lymphatics	No. ICG-Negative LVA Lymphatics	Duration of Surgery, min	Follow-up Time, d
1	57.0	F	Secondary	Pelvic cancer surgery and radiation	19.5	7	5	2	367	253
2	40.2	M	Primary	NA	28.3	5	4	1	416	93
3	61.3	F	Secondary	Pelvic cancer surgery	33.2	5	3	2	490	55
4	40.8	F	Secondary	Pelvic cancer surgery	22.3	6	4	2	390	62
5	44.4	F	Primary	NA	21.8	10	6	4	485	251

F, female; M, male; NA, not available or not applicable.

detected ICG-negative lymphatics are used for additional LVAs, in comparison to the number of LVAs without ICG-negative lymphatics. The total time of surgery varied between 367 and 485 minutes. Technically, all performed additional LVAs were feasible. Immediately after implementing anastomosis, a strong lymphatic drainage could be appreciated in all previously ICG-negative lymphatics by washout effect. Patients continued conservative treatment throughout the postoperative course. All patients reported a subjective decrease in pressure sensation and swelling. Postoperative clinical investigation (circumferential limb measurements) showed significant reduction of limb circumference. No skin infections occurred at 6 months postoperatively.

Patient 1

A 57-year-old woman with a secondary left LEL with ISL Stadium II-III had undergone pelvic and inguinal lymphadenectomy and radiation therapy for gynecologic cancer treatment in 2003. She had developed progressive lymphedema symptoms from 2010 despite following a consequent conservative therapy regimen. Symptoms included a painful sensation of pressure in the limb and nonreversible swelling (Fig. 1). A total of 7 LVAs were performed. Two LVAs were conducted with ICG-negative lymphatics. In 1 of the 7 LVAs, 2 lymphatic ducts were anastomosed to 1 vein, of which one was ICG negative (Fig. 2). Six months postoperatively, patient reported a subjectively significant decrease in pressure sensation, and clinical observations showed an increase in skin quality and signs of less swelling (Fig. 3).

DISCUSSION

One of the most crucial and in the same time difficult points in preoperative planning of LVAs is to detect patent lymphatic ducts without fibrosis and with high flow. While the scientific and clinical interest of the role of the lymphatic system in physiologic and pathologic processes has increased over the last decade, our knowledge about the lymphatic system compared with the cardiovascular system is still lacking behind. Pathophysiologic interactions, which might have a crucial impact on therapeutic strategies in cancer metastasis and lymphedema, are scientifically not completely understood so far. Indocyanine green is widely accepted as a comparatively easy and informative technique to not only detect and visualize lymphatics, but also stage lymphedema.[1–3] It has been stated

TABLE 2. Comparison Between the Total Number of LVAs With ICG-Positive Lymphatics Only and the Total Number of LVAs, if ICG-Negative Lymphatics Are Used Additionally in Each Case

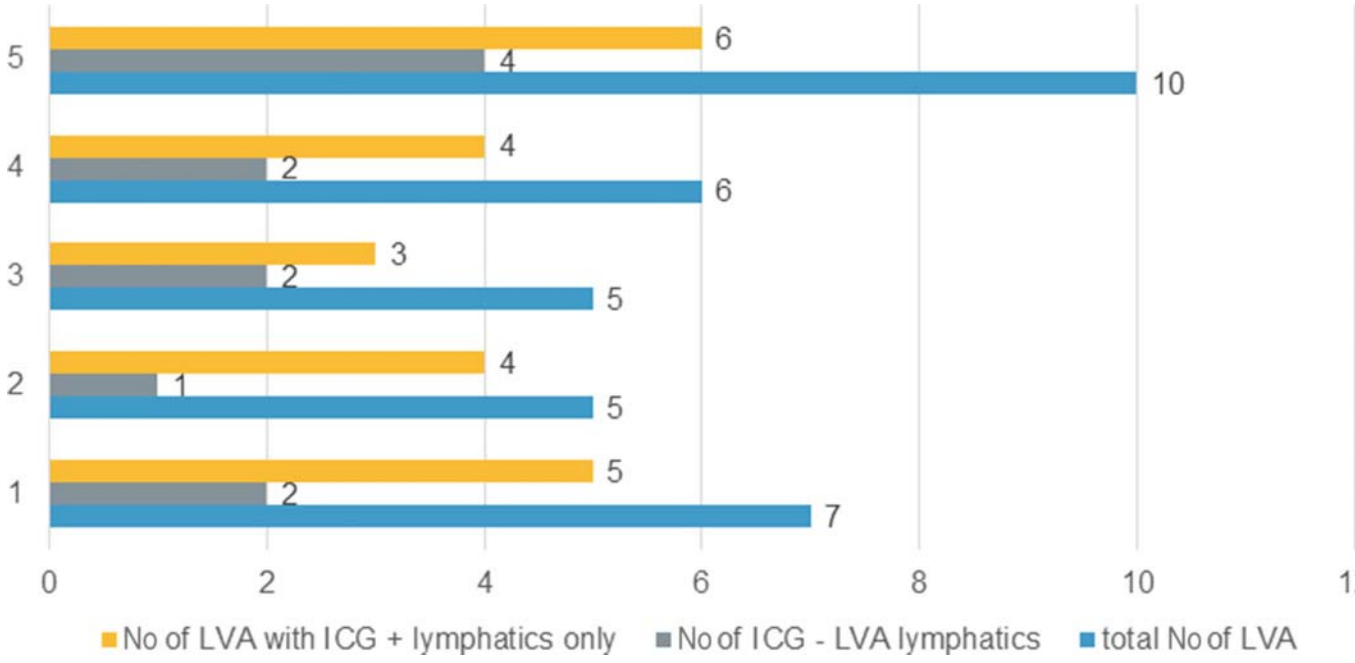

FIGURE 1. Preoperative photographs.

that ICG gives information only about the superficial subdermal lymphatics. Therefore, the lymphedema staging reported in this study might refer to only a part of the real lymphatic problem of the affected limb. Several clinical and experimental studies have reported on usefulness and limitations of ICG lymphography, and different concepts on the anatomical characteristics of the lymphatic system do exist. In order to further assist in the clinical management of lower limb lymphatic disorders, cadaver studies have been implemented to prove that divergent and alternative lymphatic drainage pathways do exist.[4,5] Recently, a new concept of lymphosomes was introduced after studying the lymphatic system in different animals and human cadavers in order to establish a better understanding of the anatomy, which is paramount for current procedures in the surgical management of cancers and lymphedema.[6] Superficial lymphatic vessels diverge and merge on their way to the lymph node and do not cross each other in humans, demarking and dividing the skin into certain lymphatic territories, which are referred to as lymphosomes. Differences in vessel depth or vessel diameter may be a contributing factor favoring transport through 1 vessel over another and thus leading to ICG-negative performance of lymphatics.[7] The impact of ICG on normal lymphatic contractility and drainage function may also introduce a significant artifact, which might explain the ICG-negative appearance of some lymphatics. In normal functional lymphatics of the extremities, ICG is quickly absorbed by the lymphatic system after intradermal injection and is rapidly transported to the groin or armpit showing a linear pattern. These lymphatic vessels are referred as patent. In advanced stages of lymphedema, differential dermal backflow patterns occur, which can help to classify severity of the disease.[8] Whenever dermal backflow is present, percutaneous detection of patent lymphatics by ICG is near impossible preoperatively. Studies have reported on the existence of large and high-flow lymphatic vessels even in ICG-negative and dermal backflow regions.[8] Weiler and Dixon[9] demonstrated differential transport functions between 2 collecting vessels in a rat model. They assumed that preferential lymphatic drainage patterns might exist such that, for a given tissue space, fluid drainage is the primary responsibility of one

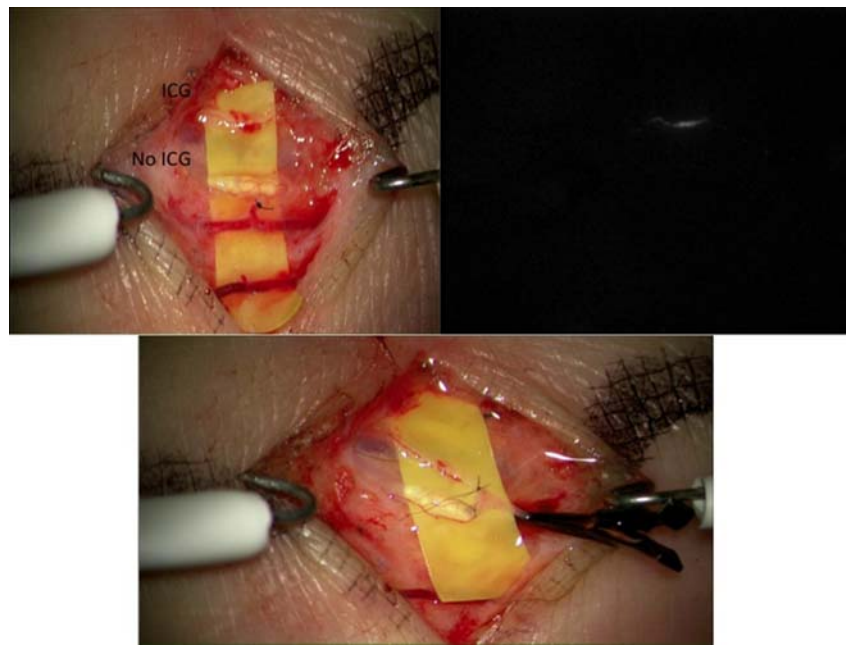

FIGURE 2. Intraoperative pictures lymphatic vessels ICG + and ICG -.

FIGURE 3. Postoperative pictures at 6 months.

single vessel, whereas any additional vessels in the area serve as overflow or reserve transport routes for large fluid loads.

To our knowledge, LVA to ICG-negative lymphatics has not been given the right amount of attention and importance in literature. So far, there is no evidence that ICG-negative lymphatics might differ in quality or effectiveness in lymphatic drainage. In our small series, if we had used ICG-positive lymphatics only, only 22 LVAs could have been implemented. However, as we have used ICG-negative lymphatics as well, 11 more LVAs could be performed. The benefit of multiple LVAs in 1 surgical setting is obvious and has been reported in literature.[10] Chances of greater and more significant drainage after LVA become higher.[11] Indocyanine green–negative lymphatics also do make these multiple LVAs possible. We would have lost the impact of 33% more LVAs on the overall outcome if we had neglected those ICG-negative lymphatics in the first instance.

Here we presented our preliminary results. One limitations of this study is the small number of cases and lack of long-term and objective results. Future clinical studies must be pursued prospectively with a larger number of subjects and with objective clinical outcomes to improve reliability of results. Comparative studies with 2 groups, in which ICG-positive LVA only and ICG-negative LVA only are implemented, should be carried out in order to investigate the role and true impact of ICG-negative lymphatics in LVA surgery. Basic knowledge of lymph dynamics is also fundamental to understand their transport and the interactions between different lymphatics.

CONCLUSIONS

Conclusions about lymphatic function should be constantly reevaluated during surgery, and clinical findings should not be neglected. Indocyanine green–negative lymphatics found intraoperatively should be evaluated for additional LVAs in order to maximize drainage effect and might provide better outcome.

REFERENCES

1. Yamamoto T, Matsuda N, Doi K, et al. The earliest finding of indocyanine green lymphography in asymptomatic limbs of lower extremity lymphedema patients secondary to cancer treatment: the modified dermal backflow stage and concept of subclinical lymphedema. *Plast Reconstr Surg*. 2011;128:314e–321e.
2. Akita S, Mitsukawa N, Kazama T, et al. Comparison of lymphoscintigraphy and indocyanine green lymphography for the diagnosis of extremity lymphoedema. *J Plast Reconstr Aesthet Surg*. 2013;66:792–798.
3. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. *Plast Reconstr Surg*. 2013;132:1305–1314.
4. Pan WR, Zeng FQ, Wang DG, et al. Perforating and deep lymphatic vessels in the knee region: an anatomical study and clinical implications. *ANZ J Surg*. 2017;87:404–410.
5. Pan WR, Levy SM, Wang DG. Divergent lymphatic drainage routes from the heel to the inguinal region: anatomic study and clinical implications. *Lymphat Res Biol*. 2014;12:169–174.
6. Suami H, Scaglioni MF. Lymphatic territories (lymphosomes) in the rat: an anatomical study for future lymphatic research. *Plast Reconstr Surg*. 2017;140:945–951.
7. Gashev AA, Nagai T, Bridenbaugh EA. Indocyanine green and lymphatic imaging: current problems. *Lymphat Res Biol*. 2010;8:127–130.
8. Narushima M, Yamamoto T, Ogata F, et al. Indocyanine green lymphography findings in limb lymphedema. *J Reconstr Microsurg*. 2016;32:72–79.
9. Weiler M, Dixon JB. Differential transport function of lymphatic vessels in the rat tail model and the long-term effects of Indocyanine Green as assessed with near-infrared imaging. *Front Physiology*. 2013;4:215.
10. Yamamoto T, Yoshimatsu H, Narushima M, et al. Sequential anastomosis for lymphatic supermicrosurgery: multiple lymphaticovenular anastomoses on 1 venule. *Ann Plast Surg*. 2014;73:46–49.
11. Campisi CC, Ryan M, Boccardo F, et al. A single-site technique of multiple lymphatic-venous anastomoses for the treatment of peripheral lymphedema: long-term clinical outcome. *J Reconstr Microsurg*. 2016;32:42–49.