The Diagnostic Unreliability of "Classic" Physical Signs of Lymphedema

Seshadri Raju, MD, FACS, Corbin May, BS, MS,
Arjun Jayaraj, MD. The Rane Center at St. Dominic Hospital

Objective: In Western populations, chronic venous disease is a major source of secondary lymphedema; as many as 30% of chronic venous disease patients may have phlebolymphedema. Proper diagnosis is particularly important in this population as clinical improvement in swelling (and even reversal of lymphatic damage in some) may be achieved by early correction of underlying venous disease. Diagnosis of lymphedema currently rests on "classic" clinical markers (dorsal hump, squaring of toes, Stemmer sign, and nonpitting edema) in most community practices. Isotope lymphangiography, which is objective, is performed infrequently to confirm the clinical impression. Once a diagnosis of lymphedema is made, the patient is invariably doomed to lifelong conservative therapy, which is often ineffective. The aim of this study was to evaluate the diagnostic accuracy of clinical signs compared with isotope lymphangiography.

Methods: During a 1-year period (2016-2017), 2699 limbs with swelling (1396 left, 1303 right) were evaluated. All limbs were prospectively scored for the classic lymphedema signs listed before. Isotope lymphangiography was routinely performed for objective evaluation. Isotope lymphangiography was scored as positive for lymphedema on the basis of time of isotope appearance in the groin lymph nodes, number of visualized lymph nodes, isotope density, presence of lymph channels, and pooling of isotope (dermal backflow).

Results: A total of 2699 limbs were evaluated with swelling. Of those, 769 underwent lymphoscintigraphy; 320 (42%) were normal and 449 (58%) were abnormal. Also, of the swollen limbs, 401 (15%) had classic clinical signs of lymphedema (dorsal hump, 53%; square toes, 25%; Stemmer sign, 16%; nonpitting edema, 6%). Among the limbs with positive clinical signs (n = 401), lymphangiography was performed on 203; 141 (69%) were positive for lymphedema and 62 (31%) were normal. Conversely, among 449 swollen limbs with abnormalities on lymphoscintigraphy, only 141 (35%) had one or more classic clinical signs. Among those with dermal backflow or pooling (n = 114), clinical signs were present in only 30 limbs (26.3%).

Conclusions: Classic clinical signs are notoriously unreliable for correct diagnosis of lymphedema. Objective lymphoscintigraphy is normal in 31% of limbs with classic clinical signs of lymphedema. This means that the edema is not lymphatic but probably of correctible venous disease; and similar clinical signs can be generated by venous disease without lymphatic damage. On the contrary, isotope lymphangiography detected an abnormality in 246 of 449 (55%) limbs with limb swelling but without classic lymphedema clinical signs. In these patients, venous intervention may be less efficacious, and the isotope test is of prognostic value. Routine use of lymphoscintigraphy is recommended in all patients with limb swelling for objective lymphatic evaluation. The practice of making a diagnosis of lymphedema on the basis of classic clinical signs should be abandoned.

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The Lymphatics in Early Venous and Peripheral Arterial Disease

John Rasmussen, PhD,[1] Banghe Zhu, PhD,[1] Aaron Sahihi,[1] Melissa B. Aldrich, PhD,[1] Stuart Harlin, MD,[1] Kristofer M. Charlton-Ouw, MD,[1] Caroline E. Fife, MD,[2] Thomas O'Donnell Jr, MD,[3] Eva M. Sevick-Muraca, PhD[1]. [1]University of Texas Health Science Center; [2]CHI St. Luke's Health; [3]Tufts Medical Center

Objective: Emerging evidence suggests that the lymphatics play an important role in the early pathogenesis and progression of peripheral venous and arterial diseases. Herein we evaluate the lymphatic anatomy and function in patients with early chronic venous disease (CVD; Clinical, Etiology, Anatomy, and Pathophysiology class C0-C4) or mild to moderate peripheral arterial disease (PAD; Rutherford class 2-5 disease) using near-infrared fluorescence lymphatic imaging (NIRFLI).

Methods: After informed consent and under a Food and Drug Administration-approved investigational new drug application for off-label administration of indocyanine green (ICG) as an imaging agent for NIRFLI, we visualized lymphatic pumping activity and lymphatic anatomy in study subjects diagnosed with early CVD or mild to moderate PAD. Subjects received two intradermal injections of ICG on the dorsum of each foot, one injection in each medial ankle, one injection on each of the medial and lateral sides of the calves, and one in the anterior thigh or near areas of vascular interest. Imaging was performed by illuminating the skin with near-infrared light and collecting the resultant fluorescent light emanating from the ICG-laden lymph. Imaging was conducted during a period of 1.5 to 2 hours.

Results: In this ongoing pilot study, we have imaged one subject with mild PAD and four subjects with early CVD (C3 and C4) to date, with an anticipated accrual of 40 subjects. In each of the four CVD subjects imaged to date, we have found evidence of lymphatic abnormalities including dermal backflow and dilated, tortuous, or segmented lymphatic vessels (Fig) as well as impaired lymphatic pumping. In the PAD subject, with Rutherford stage 3 disease, we observed an unusual pattern of nonlinear lymphatic vessels in the lateral right calf and dermal backflow across both legs. In addition, while we observed active lymphatic pumping in this subject, many of the vessels also exhibited lymphatic reflux.

Conclusions: Using NIRFLI, we have observed abnormal lymphatic anatomy and reduced lymphatic function in all subjects enrolled in this pilot study of the lymphatics in early peripheral arterial and venous diseases. Observed abnormal lymphatic anatomy, compared with previously imaged healthy subjects, included dermal backflow and segmented, dilated, and tortuous or varicose lymphatic vessels. Reduced lymphatic pumping was also observed in all subjects, and lymphatic reflux was noted in the subject with an arterial component of the disease. While this study continues, evidence is mounting that lymphatic dysfunction is associated with the cause of peripheral venous and arterial diseases.

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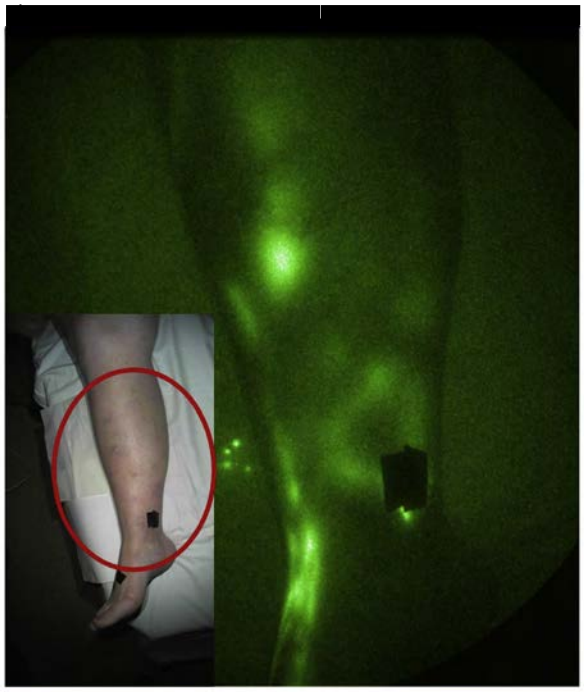

Fig. Near-infrared fluorescence lymphatic imaging (NIRFLI) of lymphatic abnormalities.

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