Diagnosis and treatment of venous lymphedema

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Background: **Chronic venous disease (CVD) is a common cause of secondary lymphedema. Venous lymphedema is sometimes misdiagnosed as primary lymphedema and does not receive optimal treatment. We have routinely used intravascular ultrasound (IVUS) imaging in all cases of limb swelling. The aim of this study is to show that (1) routine use of IVUS can detect venous obstruction missed by traditional venous testing, and (2) iliac-caval venous stenting can yield satisfactory clinical relief and can sometimes reverse abnormal lymphangiographic findings.**

Methods: **The study comprised CVD patients who underwent iliac vein stenting. Lymphangiography was abnormal in 72 of 443 CEAP C_3 limbs, with leg swelling as the primary complaint (abnormal lymphangiography group). Clinical features and stent outcome were compared with a control group of 205 of 443 with normal lymphangiography (normal lymphangiographic group).**

Results: **Clinical features were a poor guide to the diagnosis of lymphedema. Isotope lymphangiography was not helpful in differentiating primary from secondary lymphedema. Venography had 61% sensitivity to the diagnosis of venous obstruction. IVUS had a sensitivity of 88% for significant (≥50% area stenosis) venous obstruction. At 40 months, cumulative secondary stent patency was similar for the abnormal (100%) and normal lymphangiographic (95%) groups. Swelling improved significantly after stent placement in the abnormal lymphangiographic group (mean [standard deviation] swelling grade improvement 0.8 ± 1.1) but was less ($P < .004$) than in the control group (1.4 ± 1.3). Complete swelling relief was 16% and 44% ($P < .001$) and partial improvement (≥1 grade of swelling) was 45% and 66% ($P < .01$) in the abnormal and normal lymphangiographic groups, respectively. Associated pain was present in 50% and 36% of the swollen limbs in the abnormal and normal lymphangiographic groups. Pain relief (≥3 visual analog scale) at 40 months was 87% and 83%, respectively ($P = .3$), with 65% and 71%, experiencing complete pain relief. Quality of life criteria improved after stent placement in both groups but to a better extent in the normal lymphangiographic group. Abnormal lymphangiography improved or normalized in 9 of 36 (25%) of those tested after stent correction.**

Conclusions: **Prevailing practice patterns and diagnostic deficiencies probably result in the misdiagnosis of many cases of venous lymphedema as "primary" lymphedema. IVUS is recommended to rule out venous obstruction as the associated or initiating cause of lymphedema. Iliac venous stenting to correct the obstruction has excellent long-term patency and good clinical outcome, although results are not as good as in those with normal lymphatic function. (J Vasc Surg 2012; 55:141-9.)**

Lymphedema is classified into primary and secondary types. Primary lymphatic dysfunction is of congenital or idiopathic origin. Secondary lymphedema is from damage to lymphatic structures from parasites, surgery, radiation, or infection, commonly cellulitis. Secondary lymphedema from *Filariasis* has a much higher prevalence in tropical countries than the primary variety. Surgical or radiation damage to regional lymph nodes is a major source of secondary lymphedema in Western populations. When such a secondary cause is excluded, the lower limb swelling in a large group of patients is often assumed to be primary in nature.

In patients with advanced chronic venous disease (CVD), 20% to 30% will have associated lymphatic dysfunction, presumably due to secondary damage from overload or recurrent cellulitis.[1-3] The term phlebolymphedema is variably used to designate this form of lymphedema of venous origin.[4] The very high incidence of CVD in the general population would suggest that secondary lymphedema from this cause has a high relative prevalence, probably several times more than the primary variety. Yet, this is not common knowledge among primary care physicians, and limb swelling is often labeled as "primary lymphedema" on clinical grounds alone, which are unreliable (Figs 1 and 2) because they are not exclusive to primary lymphedema.

Nucleotide lymphangiography is variably performed for diagnosis, but this test by itself cannot reliably differentiate primary from secondary lymphedema[3,5] because delayed or absent node visualization can occur in either case. Venous investigations are seldom done. Compounding the problem is that duplex imaging, the main venous diagnostic modality, is insensitive to iliac vein lesions with routine technique, and venography, which is used less often, will miss as many as 50% of correctable venous pathology (Fig 3).[6-8] Intravascular ultrasound (IVUS) imaging is more definitive[9] but has not yet been adopted widely, even in specialized venous centers. As a result of these prevailing practice patterns, a large number of patients with correctable venous lesions are inappropriately consigned to lifelong compression and are often referred to physiotherapists specializing in manual drainage and decongestive therapy.[4,10]

From The Rane Center.

Competition of interest: Drs Raju and Neglén own stock in Veniti Incorporated.

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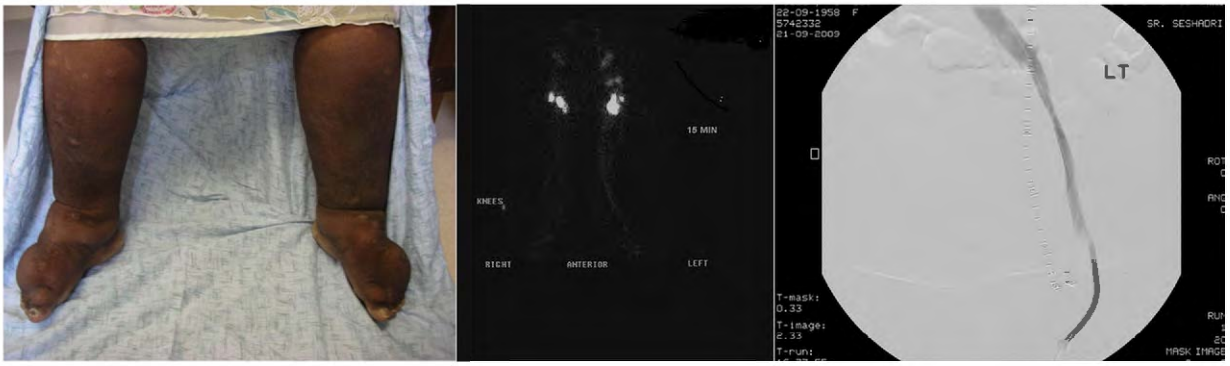

Fig 1. Swelling in the dorsum foot, squaring of toes, and Stemmer sign are widely considered "classic" clinical features of lymphedema. In our experience, these may also be present in long-standing venous swelling and are not exclusive to lymphedema (see text). **Left,** This patient was diagnosed as having "lymphedema" on clinical grounds and was treated for several decades with compression, which was ineffective. **Middle,** Isotope lymphangiography was normal. **Right,** Transfemoral venography showed postthrombotic iliac vein stenosis (left venogram is shown).

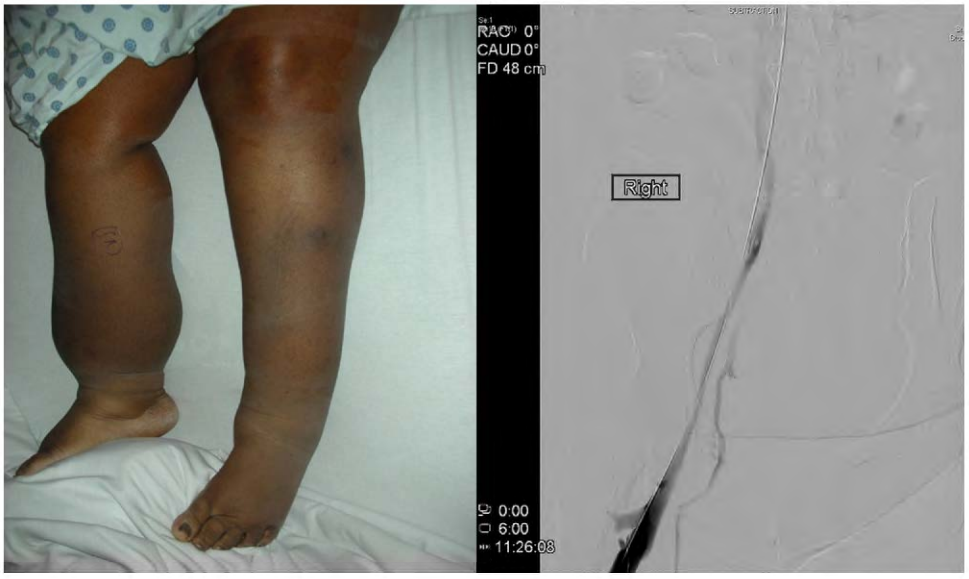

Fig 2. This patient had onset of leg swelling from early adolescence. Lymphatic delay was noted on the right side but was normal on the left. Venogram showed bilateral iliac vein stenoses. Right limb venogram is shown with severe diffuse iliac vein stenosis. Note the normal caliber of the femoral vein.

We have routinely used IVUS imaging in all patients presenting with leg swelling, regardless of positive or negative preoperative test results for venous obstruction or lymphatic function. The diagnostic yield of IVUS-positive iliac-caval-femoral obstructions is very high in these patients.[6] We present our clinical experience with 72 lymphedematous limbs with abnormal lymphangiograms and associated venous obstruction identified by IVUS imaging. All were treated with iliac vein stents, and the results are detailed in comparison with 205 similarly treated swollen obstructed limbs that had normal preoperative lymphangiograms. The objective of this study is to show that routine use of IVUS imaging can substantially increase the diagnostic yield of correctible lesions in lymphedematous limbs that might be otherwise labeled as suffering from primary lymphedema with uncorrectable underlying pathology and that stent correction of the detected lesions can yield substantial clinical relief.

PATIENTS AND METHODS

During a 13-year period (1997 to 2010), 1739 patients with symptoms suggestive of CVD underwent iliac-caval-femoral venous stenting after investigations. Isotope lymphangiography was performed in 819 of these when primary or secondary complaints of limb swelling or cellulitis were present. The result was abnormal in 201 of 819 patients (26%). In many of these 819 limbs, swelling was transient or a secondary feature associated with skin

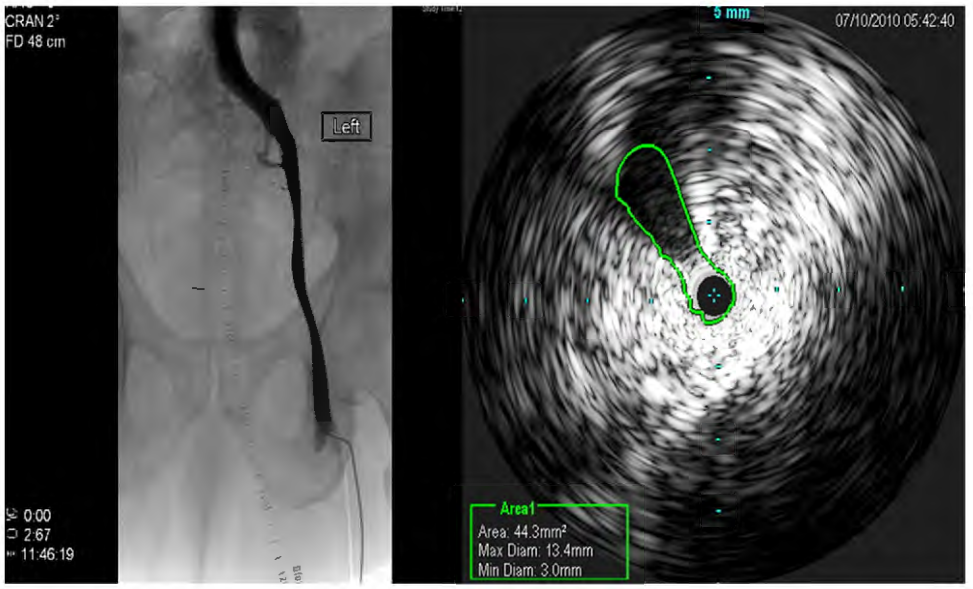

Fig 3. Venography is poorly sensitive to iliac vein obstruction. **Left,** A venogram appears unremarkable. **Right,** A tight stenosis is present, as shown by the IVUS image. Measured lumen area by IVUS planimetry was 44.3 mm^2. Normal value in adults is ~175 mm^2. A 75% stenosis can therefore be calculated to be present.

changes (eg, lipodermatosclerosis) or ulceration that would have complicated analysis for purposes of this study. To focus on swelling and swelling-related outcome, current analysis pertains only to CEAP C_3 limbs in this group (443 of 819) with swelling as the main clinical feature. The test group (abnormal lymphangiographic group) consisted of 72 of 443 (16%) of these limbs in 69 patients where preoperative lymphangiography results were abnormal. The controls were 205 limbs in the same CEAP C_3 subset with leg swelling in whom the preoperative isotope lymphangiography result was normal (normal lymphangiographic group) and that had adequate follow-up data for outcome comparisons. Associated limb pain was an additional clinical feature in both test and control groups.

The clinical and investigative evaluations of patients with suspected CVD have been described in detail previously.[11] Only those relevant to the present report are included.

Venography. Venography was by the transfemoral route, except when it was precluded by clinical or technical factors, such as renal failure, international normalized ratio >2, massive obesity, or access failure.

Isotope lymphangiography. An injection of 0.6 MCI of technetium 99M sulfur colloid was placed subcutaneously between first and second toe web space, and the progress monitored at 10, 20, and 40 minutes, or longer (up to 2 hours), while exercising the limb, for evidence of node visualization. Pooling and dermal backflow were noted when present. Assessment was based on time-related node visualization: normal when seen by 20 minutes, delayed when longer, and absent when imaging at 2 hours was negative.

Triple-dose lymphangiography. An injection of 1.8 MCI of isotope colloid was placed into the web space because a relatively large fluid depot might have diluted the isotope retarding visualization. This technique was used in 71 CVD limbs (all CEAP classes) whose normal-dose lymphangiogram showed delayed or absent node visualization. Normalization with the triple-dose technique was found in 10 limbs (14%; Fig 4), and 16 limbs were CEAP C_3 and are included in the current series.

IVUS assessment and stent placement. Only patients in whom compression or conservative therapy had failed were considered. The stenting technique has been described in detail elsewhere.[12,13] IVUS (6F) was routinely used for diagnosis and stent correction of obstructive lesions. Wallstents (Boston Scientific, Watertown, Mass) were exclusively used. Aspirin was routinely used for stent maintenance. Warfarin therapy was reserved for patients with thrombophilia, recurrent thrombosis, or previous unprovoked thrombosis. The compression regimen in place at the time of intervention was continued after stent placement.

Reinterventions to correct stent malfunction were required in 17 of 72 limbs (24%) in the abnormal lymphangiography group and in 53 of 205 limbs (26%) in the control group.[14] Stent malfunction was mostly due to in-stent restenosis or stent compression, sometimes associated with poor stent inflow/outflow as a result of new or previously missed lesions adjacent to the stent. Reinterventions included four successfully lysed stent occlusions in the control group. Reinterventional outcome is integrated into the results as reported for both groups.

Fig 4. In some cases, lymphatic delay **(left)** with standard technique will normalize if triple dose of the isotope-tagged colloid is injected **(right)**.

Outcome assessment. Patients were seen in follow-up by one of the authors (S.R. or P.N.) at 6 weeks, at 3, 6, and 12 months, and at yearly intervals thereafter. Pain assessment was by visual analog scale (VAS),[15] and swelling was assessed by subjective report of the patient (improved or not) and by objective physical examination: grade 0, none; grade 1, mild pitting or nonpitting but not obvious; grade 2, obvious swelling limited to the foot and ankle; grade 3, obvious swelling involving the limb above the ankle.

The Chronic Venous Insufficiency Quality of Life Questionnaire[16,17] was used to assess quality of life, and preoperative questionnaire results and the last assessment available after stent placement were used for analysis. A transfemoral venogram was obtained at 3 or 6 months for routine assessment of the stent and as needed when stent malfunction was suspected. Duplex assessment of the stent, using a special technique described by Labropoulos et al,[18] was performed at shorter intervals. All clinical and investigative results were entered into a time-stamped electronic medical record (EMR) system prospectively at the time of encounter and analyzed retrospectively. Because existing data were being presented in aggregate anonymous fashion, Investigational Review Board approval was not required for this study.

Statistical analysis. Individual data are given as median with range or mean ± standard deviation, unless otherwise indicated. Continuous variables were analyzed: Wilcoxon rank test for paired data, Mann-Whitney test for unpaired data, and Fisher exact test for categoric variables. Primary, assisted primary (patency after preemptive intervention), and secondary patency (patency after intervention for occlusion) rates, as defined by the reporting standards of the International Society for Cardiovascular Surgery/Society for Vascular Surgery[19] were calculated using survival analysis with the Kaplan-Meier method. Cumulative survival analysis was also used to analyze and compare recurrence of pain, swelling, and ulcer after the treatment. The log-rank test was used to compare cumulative curves. GraphPad Prism 5.03 software (GraphPad Software, San Diego, Calif) was used for analysis. Results are reported using *P* values and effect or odds ratio for continuous and categoric variables, respectively. A value of $P \leq .05$ was considered significant. The counts for individual variables may vary slightly from the aggregate number of limbs because of missing data in some fields and are shown in context.

RESULTS

Demographics and relevant clinical features of abnormal lymphangiography and control groups are reported in Table I. The abnormal lymphangiographic group was significantly younger by about a decade and had more women and slightly greater proportion of primary cases than the normal lymphangiographic group. There was no significant difference in other categories. Familial history of swelling, early or late age of onset, incidence of bilateral limb swelling, associated limb pain (or its absence), and pain severity were similar in both groups, meaning that these are not reliable discriminatory features to diagnose lymphedema.

The breakdown of physical swelling severity is reported in Table II. The median swelling grade, grade distribution, and incidence of grade 3 swelling were no different between the two groups.

In the 72 limbs with abnormal lymphangiograms, node visualization was absent in 16 (22%) and delayed in 56 (78%). Isotope pooling in the lower leg and dermal backflow was present in 14 limbs (19%).

Table I. Demographics of normal and abnormal lymphangiography groups

	Lymphangiography result		
	Abnormal	*Normal*	
Variable[a]	*(n = 72)*	*(n = 205)*	P
Body mass index	33 (17-53)	33 (18-57)	.887
Age	48 (18-86)	57 (17-91)	<.001[b]
Male:female	1:8	1:3	<.001[b]
Primary:postthrombotic	4:3	1:1	<.001[b]
Age at onset, years			
<20, %	8	4	.245
>60, %	29	29	.499
Family history of swelling, %	1	3	.142
Duration of symptoms, years	6 (0-54)	3 (0-58)	.368
Bilateral limb swelling, %	44	43	.891
Associated limb pain, %	50	36	.061
Pain level (visual analog scale)	6.23 ± 1.93	6.10 ± 1.67	.655

[a]Continuous data are shown as median (range) or as mean ± standard deviation.
[b]Statistically significant.

Table II. Swelling severity in limbs with abnormal and normal lymphangiography

	Lymphangiography result		
	Abnormal	*Normal*	
Swelling grade	*(n = 72)*	*(n = 194)*	P
Grade 1, No. (%)	7 (10)	25 (13)	.533
Grade 2, No. (%)	10 (14)	31 (16)	.845
Grade 3, No. (%)	55 (76)	138 (71)	.442
Median (range)	3 (1-3)	3 (1-3)	.651

Stented lesions were nonocclusive stenoses, except three limbs in the abnormal lymphangiographic group and nine in the control group that were recanalizations of chronic total occlusions. The disease was typically segmental in postthrombotic disease and subsegmental in "primary" pathology.[6] The common iliac vein was stented in all limbs except one in the control group, where the stent was restricted to the external iliac vein and the common femoral vein. In most cases, the stent in the common iliac vein was extended caudad into the external iliac vein or frequently into the common femoral vein because of involvement of postthrombotic disease or the presence of distal "primary" lesions at the common-external iliac junction or the inguinal ligament. The lower end of the stent was extended into the external iliac vein in 10 limbs (14%) in the abnormal lymphangiographic group and in 12 limbs (6%) in the control group, and into the common femoral vein in 59 limbs (83%) of the abnormal lymphangiographic group and in 156 limbs (76%) of the control group. The upper end of the stent was routinely extended 3 to 5 cm into the inferior vena cava for technical reasons.[11,12] The stent stack was extended even higher into the vena cava because of its involvement in primary[6] or postthrombotic disease: in 7 limbs (10%) in the abnormal lymphangiographic group and in 25 limbs (12%) of the control group.

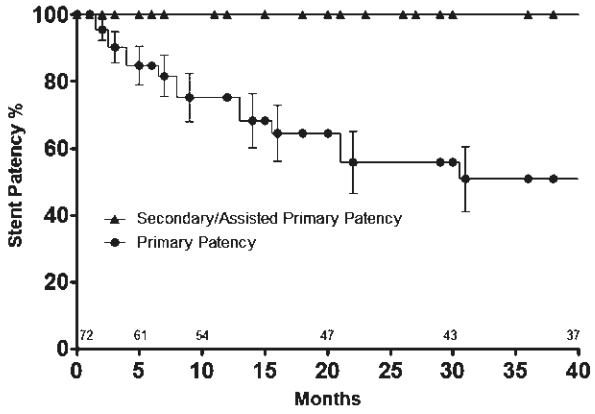

Fig 5. Cumulative stent patency in abnormal lymphangiographic group. Assisted primary and secondary patency curves were the same. The *error bars* show the standard deviation.

At 30 days there were no deaths, and procedural morbidity was minor, consisting mostly of back pain in ~25% of patients. No patients required readmission. Access site hematoma/seroma occurred in 1.5%. Stent embolization to the upper vena cava occurred intraoperatively (none later) in 2%; all were successfully repositioned/retrieved during the procedure. There was no perioperative hemorrhage requiring transfusions. Postoperative deep venous thrombosis (<30 days) occurred in one limb (1.4%) of the abnormal lymphangiographic group and in seven limbs (3.5%) of the control group combined with pulmonary embolus in one instance. All affected limbs, except one limb with calf vein thrombus in the control group, were successfully managed by thrombolysis.

Venography was poorly sensitive to the presence of obstruction in the lymphedematous group. Preoperative venography in 57 limbs was suggestive of an iliac vein lesion in 61%, including collaterals being present in 26%. Intraoperatively, obstructive lesions were detectable by IVUS in 63 of 68 limbs in the abnormal lymphangiographic group and in 165 of 191 limbs in the normal lymphangiographic group (overall 228 of 259) yielding a diagnostic sensitivity of 88% for IVUS. Although impervious to IVUS, stentable lesions were shown to be present in 31 of 259 (12%) of the limbs by balloon waisting detected on routine balloon sizing maneuvers. All IVUS missed lesions were discrete (membranous?) at or near the hypogastric vein orifice, which seemed to obscure their presence. The mean area of stenosis on IVUS planimetry (missed lesions were scored as 0% stenosis) was 70% ± 20%.

Mean follow-up was 27 ± 33 months for the abnormal lymphangiographic group and 18 ± 21 months for the normal lymphangiographic group. Cumulative primary,

Table III. Swelling outcome after stent placement in limbs with abnormal and normal lymphangiography

	Lymphangiography result		
Swelling variable[a]	*Abnormal (n = 51)*	*Normal (n = 194)*	P
Swelling grade			
Pre-stent	2.7 ± 0.6	2.6 ± 0.7	.069
Post-stent	2.0 ± 1.2	1.2 ± 1.3	<.001[b]
Swelling grade improvement	0.8 ± 1.1	1.4 ± 1.3	.004[b]
Complete swelling relief	8 (16)	86 (44)	<.001[b]
Relief grade	23 (45)	127 (66)	.010[b]

[a]Continuous data are presented as mean ± standard deviation; categoric data as number (%).
[b]Statistically significant.

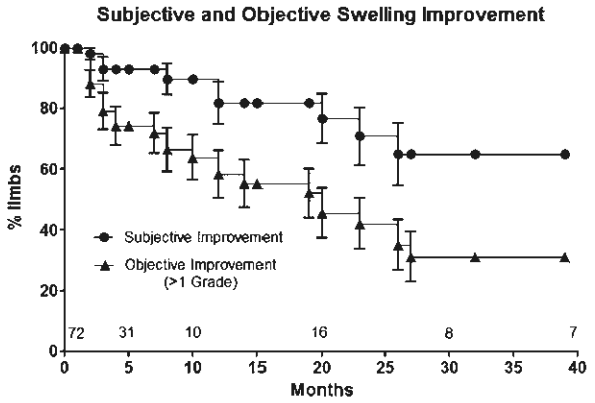

Fig 6. Swelling relief (cumulative) is shown after stent placement in lymphedematous limbs. Separate curves are shown for subjective relief, as reported by the patient, and for objective relief by examination. The difference in the curves may partly be due to metrics (see text). The *error bars* show the standard deviation.

primary assisted, and secondary stent patency rates at 40 months were 51%, 100%, and 100% in the lymphedematous group (Fig 5) and 51%, 95%, and 95% in the control group (curves not shown). These curves did not differ between the two groups ($P = .2775$, log-rank Mantel-Cox).

Swelling improvement after iliac vein stenting is reported in Table III and Fig 6. Although objective swelling improved after iliac vein stenting, the degree of partial or complete improvement was less in the abnormal lymphangiographic group than in the control group.

Most patients in both groups were noncompliant with compression stockings, in line with previous observations.[19] At follow-up, only 25 of 72 (35%) in the abnormal lymphangiographic group and 57 of 205 (28%) in the control group were wearing compression stockings.

Poststent lymphangiograms to assess improvement were available in 36 limbs with abnormal preoperative lymphangiography. Functional normalization (Fig 7) was seen in 7 limbs (19%), with improvement in an additional 2 limbs (6%), for a total of 25%.

There was significant pain relief ($P < .001$) in both groups after iliac vein stenting; cumulative pain relief was similar in the two groups (curves not shown; $P = .8$, log-rank Mantel-Cox). There was pain relief of at least 3 points in the 10-point VAS scale in 85% and 91% of patients in the abnormal and normal lymphangiographic groups, respectively. Mean VAS pain level declined from 6.3 ± 1.9 to 2.0 ± 3.3 in the abnormal lymphangiographic group and from 6.1 ± 1.7 to 0.6 ± 1.7 in the control group ($P < .4$). There was complete pain relief in 69% and 86% of patients in the abnormal and normal lymphangiographic groups, respectively ($P < .06$).

Quality of life data comparisons between the test and control groups are reported in Table IV. The sample size in the abnormal lymphangiographic group is small. Activity improved significantly in the abnormal lymphangiographic group. Pain, activity, and sleep parameters improved in the normal lymphangiographic group but not social or morale metrics. Overall scores showed an improving trend but did not reach statistical significance ($P = .08$) in the abnormal lymphangiographic group. Overall scores were significantly improved ($P < .001$) in the normal lymphangiographic group.

DISCUSSION

Limb swelling completely cleared in one in six patients with abnormal lymphatic function in this series, and about half had objective improvement in swelling. Pain relief was more substantial and more widespread. Although these clinical benefits clearly warrant stent treatment, the swelling outcome was less than in the control series with normal lymphatic function; quality of life criteria, although improved after stent placement, were less than in the control series. Nonreversible ongoing lymphatic dysfunction is the likely cause for these differences. As a clinical impression, swelling extent and severity was greater in the abnormal lymphatic group, although this was not possible to document (see below).

Subjective improvement in limb swelling was reported by two-thirds of patients with abnormal lymphangiography, but objective improvement could be confirmed in only less than half the patients. A placebo effect is an obvious explanation. But there are metrics problems with current grading of swelling severity, which lacks adequate resolution to measure improvement within the grade. In massive grade 3 swelling (Figs 1 and 2), improvement may be substantial, yet still remain grade 3, thus not allowing documentation of objective improvement. For example, swelling involving the thigh and legs will be classified as grade 3, even after swelling recedes to below the knee. Such improvement may be significant enough to allow better mobility, climb stairs, or abandon a wheel chair existence. Swelling is better tolerated if associated pain is relieved.

The grading system implies that there is a stepwise progression of swelling from foot and ankle (grade 2) to involve the rest of the lower limb (grade 3). In our clinical experience, the foot, leg, and thigh may act as separate compartments for swelling in some patients. After iliac vein

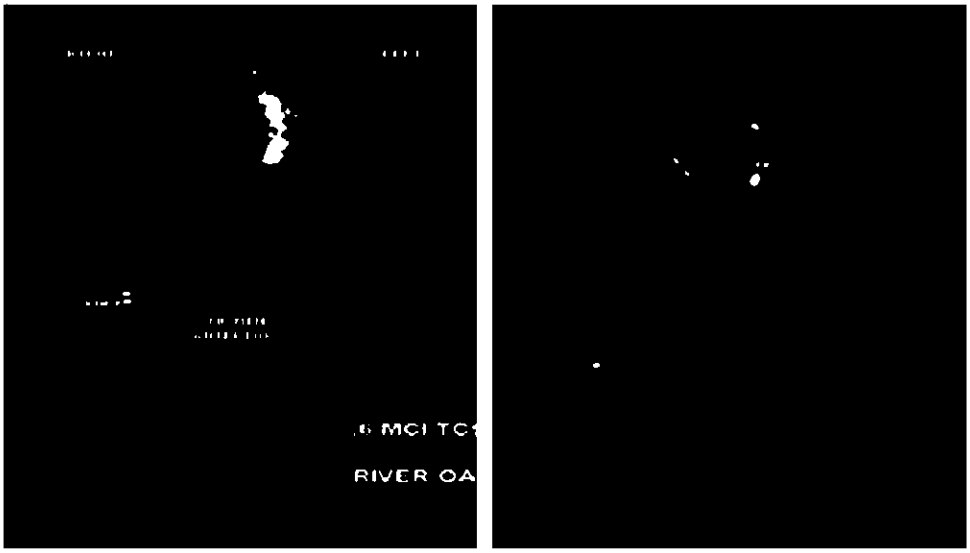

Fig 7. Left, Lymphographic nonvisualization of inguinal nodes in a patient with right-sided lymphedema. **Right,** After iliac vein stent placement, nodes promptly visualized at 20 minutes.

Table IV. Chronic Venous Disease Quality of Life Questionnaire (*CIVIQ*) outcome in limbs with abnormal and normal lymphangiography

CIVIQ category[a]	*Preoperative* Median (range)	*Postoperative* Median (range)	P
Lymphangiography result			
Abnormal (n = 25)[b]			
Pain intensity	3 (1-5)	2 (1-5)	.118
Activity limits	3 (1-5)	2 (1-5)	.007[c]
Sleep problems	3 (1-5)	2 (1-5)	.174
Social	2 (1-5)	3 (1-5)	.096
Morale	3 (1-5)	2 (1-5)	.393
Total	52 (20-100)	44 (20-100)	.078
Normal (n = 67)[b]			
Pain intensity	3 (1-5)	2 (1-5)	.001[c]
Activity limits	3 (2-5)	2 (1-5)	<.001[c]
Sleep problems	3 (2-5)	2 (1-5)	.004[c]
Social	3 (2-5)	2 (1-5)	.096
Morale	3 (1-5)	2 (1-5)	.227
Total	60 (44-100)	44 (28-96)	<.001[c]

[a]Scores for outcomes for each category range from 2 (best) to 5 (worst).
[b]Data available for questionnaires before and after stent placement.
[c]Statistically significant.

stenting, one or the other may resolve with residual swelling in the other compartment. Foot swelling is relatively poorly tolerated compared with the ankle and the leg above in some patients, particularly women, where the ability to wear proper shoes is a significant consideration. Foot swelling may resolve with clinical benefit even though residual swelling above persists in obese and lipedematous patients. Residual swelling in the plantar region is annoying to many patients, yielding an uncomfortable sensation of walking on a spongy surface.

It would seem that objective improvement in limb swelling can be reliably assessed by limb volume plethysmography. Plethysmographic techniques have been shown to be accurate in the controlled setting of physiologic laboratories. In clinical practice, tape measurements are widely used, but single point measurements are unreliable. Measurements over multiple anatomically fixed points are necessary, a task that becomes even more difficult when swelling involves the entire limb, not merely below the knee. A variety of other techniques have been described to measure limb edema, but many have not been validated or are too complex or expensive for routine use.[20,21] A practical difficulty even with validated techniques in the clinical setting is that extravascular fluid volume undergoes cyclical changes over days or weeks and intraday limb volume has a pronounced diurnal variation. An early version of the Venous Clinical Severity Score scoring system was based (time of day to reach maximum swelling) on this well-known clinical observation. This means that measurement has to be done at the same time of the day for valid comparison.

Compression stockings can be helpful when properly used in patients when limb swelling is not massive. Patient noncompliance with compression is notoriously high, even in the presence of severe symptoms, and medical supervision and patient education have not resulted in better compliance.[19] Manual drainage and decongestive therapy are effective techniques when properly administered.[22] Massage techniques do not correct the basic pathology, however, and intensive lifelong daily compliance is necessary. In venous lymphedema, it is best used in conjunction with correction of venous pathology.

Isotope lymphoscintigraphy has replaced the older contrast lymphangiographic technique because of its relative simplicity and technical ease. Magnetic resonance lymphangiography is an emerging technique but has

not received regulatory approval in the United States. Lymphangiographic assessment is based on gross visual inspection, which may not always be reliable.[5] A variety of metric enhancements of the technique can yield more precise information, but the methodology is rather complex and unsuitable for routine use.

Visual lymphoscintigraphic assessment has not been standardized, and a variety of parameters have been variably used such as the number and appearance of lymphatic channels, nodal intensity, and number of nodes visualized.[3,5,10] Time for node visualization is the most widely used metric, as in the current study, although different time scales have been used by different authors. Stagnation of the isotope in tissues and dermal backflow are also universally recognized indicators of impaired function. Delayed or absent node visualization may be due to transport failure at one or more locations in the lymphatic pathways: microlymphatics near the capillaries, larger precollectors, and the collectors themselves arborizing with regional lymph nodes. Transport failure in venous disease is at the level of microlymphatics. The collectors and nodes themselves retain their functional competence,[5,23] except when secondary damage from age (decreased function),[5] cellulitis, or the hypertrophic reaction of collector vessels to lymph stasis is superimposed. The cause of microlymphatic damage is presumed to be due to overload use or involvement in the microvascular inflammatory cascade that besets CVD.

Current and previous work[24] with a more diffuse patient population (all CEAP classes were included) show that restoration to normal lymphatic function is possible if the underlying CVD pathology is corrected. Early correction may be important because lymph stasis itself perpetuates lymphatic damage, which may become irreversible at some stage. The current series likely included limbs with irreversible primary lymphedema with coincident venous obstruction. Because venous obstruction is ubiquitous[25] in the general population, coincidence is to be expected. In either case, it would seem important to identify and correct venous obstruction as a contributory cause to leg swelling and lymphatic damage.

CONCLUSIONS

CVD is a common disease. That a third or more patients with CVD[1,2] will have lymphatic dysfunction by isotope lymphangiography suggests that this form of secondary lymphedema is probably several times more common than the primary variety. Venous pathology therefore should be ruled out before labeling lymphedema as of primary cause. Clinical features, isotope lymphangiography, routine duplex imaging, and venography cannot reliably rule out a venous cause. New diagnostic modalities, such as high-resolution imaging and enhanced duplex techniques,[18] are in evolution, but their diagnostic sensitivity has not been established. We suggest that IVUS be routinely used before referring patients to conservative therapy on the premise that the disease is primary lymphedema.

AUTHOR CONTRIBUTIONS

Conception and design: SR, PN
Analysis and interpretation: SR, PN
Data collection: JF, SR
Writing the article: SR
Critical revision of the article: SR
Final approval of the article: SR
Statistical analysis: SR, JF
Obtained funding: SR
Overall responsibility: SR

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