High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: A permissive role in pathogenicity

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Purpose: **Nonthrombotic iliac vein lesions (NIVL), such as webs and spurs described by May and Thurner, are commonly found in the asymptomatic general population. However, the clinical syndrome, variously known as May-Thurner syndrome, Cockett syndrome, or iliac vein compression syndrome, is thought to be a relatively rare contributor of chronic venous disease (CVD), predominantly affecting the left lower extremity of young women. The present study describes the much broader disease profile that has emerged with the use of intravascular ultrasound (IVUS) scanning for diagnosis and analyzes stent placement outcome in two specific NIVL subsets that may offer clues to their pathogenic role.**

Methods: **Among 4026 patients with CVD symptoms spanning the range of CEAP clinical classes, IVUS examinations were selectively done in severely symptomatic patients for indications as described. Iliac vein obstructive lesions were found in 938 limbs of 879 patients; 53% of the limbs had NIVL, 40% were post-thrombotic, and 7% were a combination. Stents were placed in 332 limbs in 319 patients in two NIVL subsets. The subsets, one with and one without associated distal limb reflux, were compared. Reflux was left untreated in the first subset.**

Results: **The median age was 54 years (range, 18 to 90 years). The female–male ratio was 4:1 and the left–right ratio was 3:1. NIVL lesions in the iliac vein occurred at the iliac artery crossing (proximal lesion) and also at the hypogastric artery crossing (distal lesion), a new IVUS finding. Venography was only 66% sensitive, with 34% of venograms appearing "normal." IVUS had a diagnostic sensitivity of >90%. The cumulative results observed at 2.5 years after stent placement in the NIVL subsets with reflux and without reflux, respectively, were complete relief of pain 82% and 77%, complete relief of swelling 47% and 53%, complete stasis ulcer healing 67% and 76%, and overall clinical relief outcome 75% and 79%. These results are nearly identical between the two subsets even though distal reflux remained uncorrected in the NIVL plus reflux subset.**

Conclusions: **NIVL has high prevalence and a broad demographic spectrum in patients with CVD. Similar lesions in the asymptomatic general population may be permissive of future development of CVD. Stent placement alone, without correction of associated reflux, often provides relief. (J Vasc Surg 2006;44:136-44.)**

Virchow[1] attributed the increased left-sided predilection of deep venous thrombosis to left iliac vein compression by the crossing artery. In 1908, McMurrich[2] first reported the presence of web-like intrinsic intraluminal lesions in 33% of 107 unselected cadavers. Subsequent large autopsy series[3–5] confirmed the surprisingly high prevalence of the lesion in the asymptomatic general population. There is disagreement if the lesions are ontogenic at embryonic venous fusion sites[6] or traumatic from the pulsations of the overlying artery. A post-thrombotic etiology appears to be ruled out,[4,5] even though instances of secondary thrombosis apparently induced by the lesions are well documented.[7,8]

Corrosion cast and venographic studies suggest that the incidence of extrinsic compressive lesions may be even more pervasive than intrinsic lesions.[5,7] Recent imaging data[9] indicate that compression of the left iliac vein at the arterial crossover point may be present in 66% of the general population without any venous symptoms. Because imaging methods, including intravascular ultrasound (IVUS), cannot differentiate intrinsic from extrinsic lesions with sufficient clarity, the generic term *nonthrombotic iliac vein lesion* (NIVL) is used throughout this report to be inclusive of both types of lesions.

Despite the widespread prevalence of the lesion in the general population, the clinical syndrome (iliac vein compression syndrome, May-Thurner syndrome, or Cockett syndrome) is thought to be a relatively rare cause of chronic venous disease (CVD), responsible for only 1% to 5% of cases.[10] The diagnosis is often established by venography in selected cases fitting the classic clinical profile described by Cockett and Thomas[11] of severe left limb symptoms of pain and swelling in young women. The diagnostic sensitivity of venography for nonthrombotic iliac vein type lesions is known to be poor.[5] Liberal use of the more sensitive IVUS[12,13] yields a more diverse picture of the syndrome than previously appreciated; particularly, we found the incidence of nonthrombotic iliac vein type lesions to be very high in symptomatic CVD cases. The question then arises if these lesions are pathogenic in CVD or simply incidental findings. Outcome data after successful stent correction of the lesions in two specific subsets described below suggests that NIVLs may play a permissive role in the development of CVD.

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MATERIAL AND METHODS

From 1996 to 2004, 4026 new patients with CVD symptoms spanning all CEAP[14] clinical classes were evaluated. Patients with nonvenous causes of limb symptoms were excluded. Detailed investigations and later IVUS examinations were selectively carried out in severely symptomatic patients for indications as outlined below. Significant proximal venous outflow obstruction was found by IVUS examination in 938 limbs (879 patients), which were treated by stent placement. The etiology of obstruction was classified as NIVL in 493 limbs (53%), as post-thrombotic disease (PTS) in 377 limbs (40%), and as mixed in 68 limbs (7%) by distinctive IVUS appearance (see later) supplemented by ancillary clinical data, such as prior deep venous thrombosis, and venographic and duplex features. The nonthrombotic–thrombotic disease ratio was 5:4. This study pertains only to limbs with NIVL; limbs with PTS lesions were excluded. Limbs with features of both NIVL and PTS were assumed to be primary NIVL complicated by thrombosis and were excluded as well because they behave like other PTS cases in clinical features and outcome.

All 493 limbs underwent stent placement, some with additional procedures for treatment of reflux, typically percutaneous saphenous ablation. The 110 limbs in the latter combined procedure group and 51 other limbs that developed significant in-stent restenosis (>20% stenosis) were excluded from analysis as the aim was to compare the outcome of successfully corrected NIVLs in the two targeted subsets unadulterated by concurrent procedures or impaired stent patency.

Correction of NIVLs by stent treatment may offer clues to their pathogenic role and reflected in the differential outcome in the two subsets. This study therefore focuses on a cohort of 332 of 493 limbs with NIVLs in 319 patients treated by stent placement alone that were functioning well during the observation period. These limbs were divided into two subsets: (1) NIVL limbs with concurrent superficial or deep reflux, or both, that were stented with the reflux component left untreated during the observation period (n = 151) and (2) limbs with NIVL alone, without associated reflux, that were also stented (n = 181).

Details of clinical presentation, workup, indications, stent technique, and results of treatment have been presented at length elsewhere[15–17] and will not be repeated here except briefly in context.

Investigations. In general, detailed investigations were performed only in CEAP[14] clinical severity ≥class 3, that is, limbs with significant (grade 3) edema, stasis skin changes, ulceration, or a combination. Exceptions were limbs with recurrent cellulitis or limbs with severe diffuse venous pain that were also considered regardless of CEAP class (ie, CEAP 0 to 2 were also considered). Diffuse venous pain means generalized orthostatic or claudication type but not pain localized only to varices. Pain was severe if ≥5 on an analogue scale or required daily use of nonsteroidal or narcotic medication for relief. Pain is not adequately covered by CEAP classification. Some patients in C3 with swelling and C4 clinical class with hyperpigmentation have little pain, do not rate their symptoms as severe, and are not candidates for a stent procedure. Conversely, even minimal swelling could be disabling if painful, particularly in elderly patients who are unable to apply compression because of frailty or arthritis.

The patients who were selected underwent a comprehensive set of venous laboratory tests, including duplex scan, ambulatory venous pressure measurement (% drop, venous filling time [VFT]), air plethysmography venous filling index (VFI_{90}) and contrast studies. A valve closure time >0.5 seconds on duplex scan was defined as reflux and graded by reflux segment score,[18] VFT, and VFI_{90}. Investigations related to iliac vein obstruction were duplex scanning (↓ phasicity),[19] arm/foot pressure test,[19] and transfemoral venography with measurement of exercise femoral pressures.[20] The latter tests have varying degrees of sensitivity and specificity. They are helpful when results are positive but are not definitive. IVUS is the gold standard to detect iliac vein obstruction.[13]

IVUS examination and stent placement. IVUS examination and possible concurrent stent placement were considered in patients who had severe symptoms interfering with work or daily living and had failed conservative therapy. Patients undergoing IVUS fell into one of two broad categories:

1. Iliac vein pathology was suspected (estimated 80% of limbs) from one or more of the investigations, whether associated with significant distal reflux or not, and
2. Results of investigations for iliac vein obstruction were negative (estimated 20% of limbs) but clinically suspected because detected distal reflux was either minimal (eg, single segment reflux) or altogether absent in the context of severe symptoms.

Technique. The IVUS system (EndoSonics, Pleasanton, Calif or Sonicath, Boston Scientific, Natick, Mass) used a 6F transducer-mounted catheter threaded on a 0.32-inch guidewire (Glidewire, Terumo, Somerset, NJ) inserted percutaneously. The iliac venous segment was assessed by on-table single-plane transfemoral venography, IVUS, and finally, balloon sizing (14- to 16-mm balloon inflated to 1 atm pressure to detect waisting) because lesions were occasionally impervious to even IVUS.

NIVLs and PTS lesions have distinctive IVUS features and are easily differentiated. PTS lesions are segmental, involving at least one entire segment (eg, common iliac vein) and often adjacent segments as well (eg, external iliac and femoral veins), because the thrombus typically propagates to the next large tributary. PTS lesions are irregular, multiple, and diffuse with wall fibrosis and lumen stenosis in the entire vein segment; trabeculae may be present. In contrast, NIVLs are subsegmental and focal (<2 cm), they occur at or near arterial crossover points near the upper or lower ends of the vein segment, and wall thickness and lumen size of the rest of the vein segment are normal. Lesions of mixed appearance (7%) were classified as NIVL-induced PTS and excluded.

When an NIVL was found, the lesion was balloon-dilated and always stented with a 14- to 16-mm Wallstent (Boston Scientific) because restenosis was universal otherwise.[15,17] On venography, the degree of obstruction could be recorded as the diameter of the stenotic area/the diameter of the normal vein below the stenosis ×100 (%). On IVUS, the built-in software program allowed the actual transverse lumen area to be outlined and measured, giving an absolute value (cm^2) and a comparison with the area below the stenosis.

Clinical follow-up. Patients were treated on an outpatient basis (23-hour admission). Those patients compliant with compression devices were encouraged to attempt abandoning them after 3 weeks postoperatively, as compressive regimens were a quality-of-life issue with many. Noncompliant patients were not fitted with new stockings.

Patients were examined at 6 weeks, 3 months, 6 to 9 months after stent placement, and at yearly intervals thereafter. Venography or duplex ultrasound scans, or both, were used to assess stent patency during the first 6 months and then annually.

The degree of swelling was assessed by physical examination (grade 0, none; grade 1, pitting, not obvious; grade 2, ankle edema; and grade 3, obvious swelling involving the limb). The level of pain was measured by the visual analogue scale method.[21] Swelling and pain outcome comparisons, as shown in cumulative graphs, are based on complete relief (grade 0 swelling and 0 level of pain) because they provide clear clinical end points. Ulcer healing was defined as complete epithelialization. Overall outcome was graded after reporting standards[14] as follows: grade 3, excellent result, asymptomatic; grade 2, good result with mild residual symptoms; grade 1, some improvement with substantial residual symptoms; grade 0, no relief, unchanged from before.

Data analysis. Clinical data were entered prospectively into a time-stamped electronic medical records program for retrospective analysis. The commercially available statistical program Graph Pad Prism 3.0 (GraphPad Software, San Diego, Calif) for Windows (Microsoft, Redmond, Wash) was used for statistical analysis. Nonparametric Wilcoxon rank sum test for unpaired data and the χ^2 test were used to compare groups as appropriate. Cumulative curves using the Kaplan-Meier method were used to analyze and compare clinical outcome. Log-rank test was used to assess significance between cumulative curves. $P < .05$ was considered significant.

RESULTS

The 319 patients in the two subsets included in this study were a median age of 54 years (range, 18 to 90 years) (Fig 1). The female–male ratio was 4:1. Bilateral stents were placed in 13 patients (4%) resulting in 332 treated limbs. The left–right limb ratio was 3:1. Specific characteristics of the two subsets with and without reflux are detailed in Table I.

The clinical presentation spanned the spectrum of C classification: C_1, 1 (0.3%); C_2, 34 (10%); C_3, 183 (55%); C_4, 69 (21%); C_5, 6 (2%); and C6, 39 (12%). The 35 patients in C_1 and C_2 had severe pain. Patients had varying combinations of pain, swelling, or stasis skin changes. Pain was absent in 27% and 22%, and swelling was absent in 22% and 17% of the limbs preoperatively in the two subsets with and without reflux, respectively. The distribution of reflux in the NIVL plus reflux subset was superficial reflux, 32%; deep reflux, 20%; and combined superficial and deep reflux, 38%. Perforators (≥4 mm) were present in 11%: 1% with deep reflux, 4% with superficial reflux, and 6% with superficial and deep reflux. Axial deep reflux to the calf was present in 30% of the limbs with deep reflux. Median reflux segment score was 2 (range, 1 to 7). VFT was significantly shorter and VFI_{90} greater in the NIVL plus reflux subset (Table I).

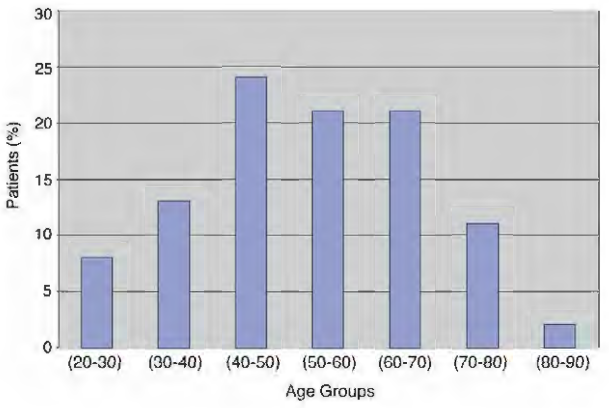

Fig 1. Age distribution of 319 patients with nonthrombotic iliac vein lesions. The median age was 54.

Distinct venographic stenosis in the frontal projection at the proximal (common iliac vein) site, the iliac artery crossover point, was present in only 23% of limbs. In another 20% of limbs, less obvious signs such as contrast translucency, lumen broadening or pancaking, or contrast irregularities suspicious of intraluminal webs or strictures, or a combination, were present (Fig 2). Axial, transpelvic, or ascending lumbar collaterals were present in 36% of limbs. Venography with one or more of the above features was abnormal in 66% of limbs. In the remaining limbs (34%), single-plane venograms were interpreted as "normal."

IVUS findings. A single proximal NIVL was present in the common iliac vein in 36% of limbs (n = 255). [Accurate record of distribution of proximal and distal lesions started only after May 2001.] In 8% of cases, a single distal NIVL was found at or near the internal iliac vein junction; in 46% the distal lesion occurred with the proximal lesion. The proximal NIVL was typically very focal (±1 cm) on the left side and was located at the iliac-caval junction; the right proximal NIVL was less focal (≤2 cm) and was located 1- to 2-cm distal to the iliac-caval junction. The proximal NIVL was three times more frequently observed on the left side, whereas the distal NIVL was equally

Table. Demographics, intravascular ultrasound findings and preinterventional hemodynamics in stented limbs with nonthrombotic iliac vein lesions with and without venous reflux

Parameter	NIVLs with reflux (n = 151)	NIVLs without reflux (n = 181)
Age, years	56 (20-85)	51 (18-90)*
Female–male ratio	110:36 (3.1:1)	146:31 (4.7:1)†
Left–right limb ratio	105:46 (2.3:1)	136/45 (3:1)†
IVUS degree of stenosis (%)	70 (0-95)	70 (0-100)†
Stenotic area (cm^2)	0.66 (0.15-2.00)	0.53 (0.02-1.65)*
Ambulatory venous pressure		
% drop	77 (0-97)	77 (0-99)†
Venous filling time (s)	23 (2-132)	44 (0-165)‡
APG:VFI_{90} (mL/s)	2 (0-12.3)	0.9 (0.0-6.0)‡
Hand-foot pressure differential (mm Hg)	1 (0-8)	1 (0-10)†
Dorsal foot hyperemia pressure differential (mm Hg)	6 (0-26)	5 (0-23)†

NIVL, Nonthrombotic iliac vein lesions; *IVUS,* intravascular ultrasound; *APG,* air plethysmograph.
Data are presented as ratios or median (range).
*$P < .01$.
†Not significant.
‡$P < .001$.

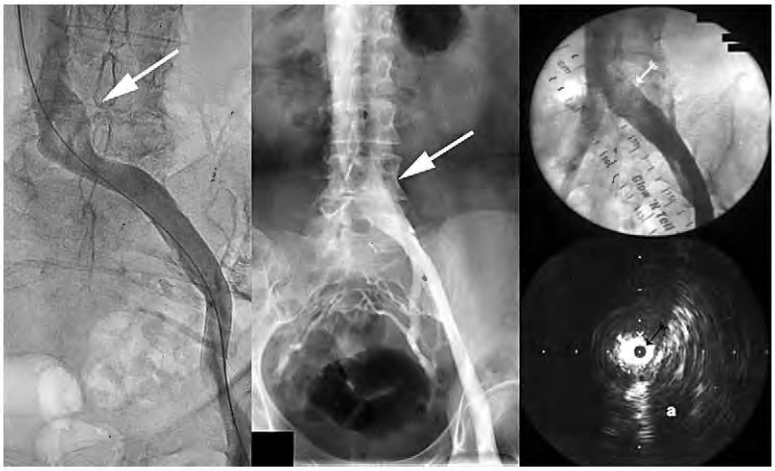

Fig 2. Variable venographic appearance of nonthrombotic iliac vein lesions (NIVLs). **Left,** "Classic" appearance with contrast translucency appearing as a filling defect *(arrow)*. **Middle,** Broadening (pancaking) of the vein with collaterals *(arrow)*. **Right,** the venogram appears entirely normal in about a third of cases. Note the absence of collaterals. However, an intravascular ultrasound (IVUS) scan showed a tight lesion *(inset)* with the lumen not larger than the 6F IVUS catheter *(arrow)*; "a" denotes adjacent artery. The *arrow* in the venogram points to the general area where the IVUS found the NIVL.

distributed bilaterally. The median area of the more severe stenosis (proximal or distal), as measured by IVUS, was 0.58 cm^2 (range, 0.02 to 2.00 cm^2; normal, ≥1.5 cm^2) representing approximately 70% stenosis. These data include some lesions (<5%) with "normal" IVUS luminal area that were detected only by balloon sizing. These lesions were graded as zero stenosis in calculation of IVUS stenoses (Table I). Most NIVLs were "soft" compared with PTS or arterial lesions, with waisting of the balloon often relieved at ≤2 atm.

Clinical results. There was no operative (30-day) mortality. Postintervention clinical evaluation was available in 90% of patients (298/332), with follow-up to 7 years (median, 10 months; range, 1 to 85 months). The data set was adequate to construct cumulative curves extending to 2.5 years. There was a substantial, statistically significant symptom improvement in the entire study group, but also in each subset after stent placement, despite presence of untreated venous reflux in one subset. The data showing cumulative rate of symptom relief, as presented in Figs 3 and 4, represent only limbs that had preoperative pain or swelling, respectively, for the two subsets. Limbs that did not have the specific symptom preoperatively (see earlier) are not included. The curves are nearly identical, with no statistical difference (log-rank test, $P = 0.17$ and 0.62, respectively). In NIVL with reflux and NIVL without reflux subsets, respectively, 82% and 77% were completely freed of swelling, and 47% and 53% were completely freed of pain at 2.5 years.

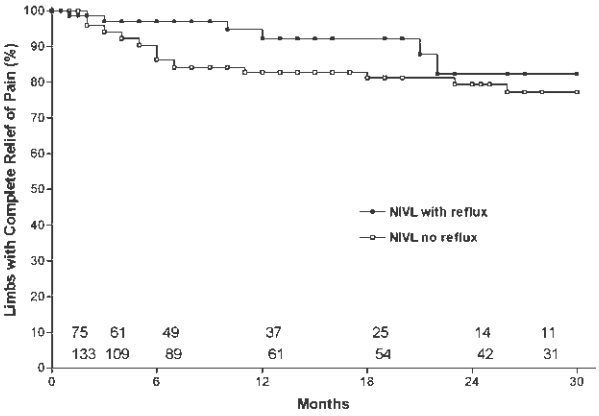

Fig 3. Pain relief after stent placement alone in nonthrombotic iliac vein lesion *(NIVL)* subsets with and without reflux. The cumulative curves represent limbs (%) with complete relief of pain. Only limbs that had preoperative pain are shown. At 2.5 years, 82% and 77% of limbs in the two subsets, respectively, were totally free of pain. There is no statistical difference between the curves. Limbs at risk at various time intervals for each subset are shown at the bottom of the graph (all SEM <10%).

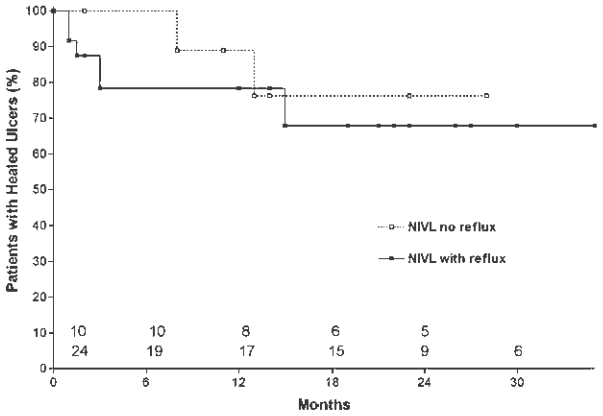

Fig 5. Cumulative complete ulcer healing following stent placement in nonthrombotic iliac vein lesion *(NIVL)* subsets with and without reflux. Reflux was *not* corrected in the latter subset, yet 67% of ulcers remained completely healed at 2.5 years. Ulcer healing was 76% in the subset without reflux at 2.5 years. There is no statistical difference between the curves. Limbs at risk at various time intervals for each subset are shown at the bottom of the graph (SEM <10% solid line; SEM >10% hashed line).

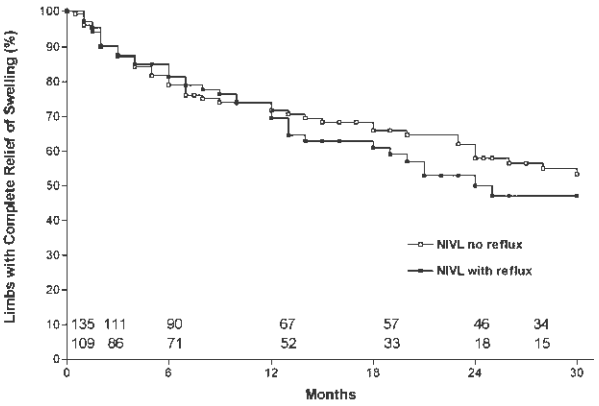

Fig 4. Swelling relief following stent placement alone in nonthrombotic iliac vein lesion *(NIVL)* subsets with and without reflux. Only limbs with preoperative swelling are shown. The cumulative curves represent limbs (%) with complete relief of swelling. At 2.5 years, 47% and 53% of limbs in the two subsets, respectively, were totally free of swelling. There is no statistical difference between the curves. Limbs at risk at various time intervals for each subset are shown at the bottom of the graph (all SEM <10%).

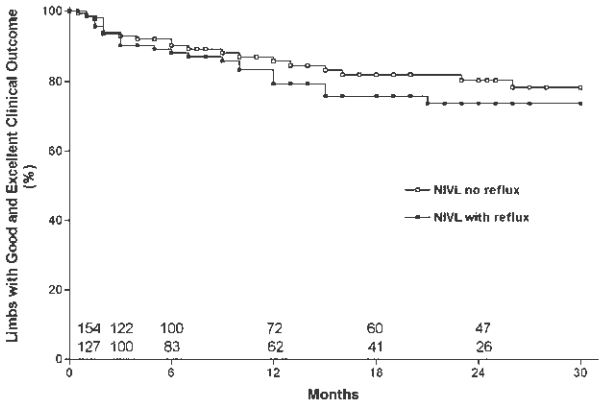

Fig 6. Overall symptom relief following stent placement in nonthrombotic iliac vein lesion *(NIVL)* subsets with and without reflux. Each curve (cumulative) represents limbs with grade 3 or 2 (excellent or good) outcomes for the specific subset. The curves are nearly identical. Limbs at risk for each subset at various time intervals are shown at the bottom of the graph (all SEM <10%).

Active stasis ulcers were seen in 39 limbs (29 limbs with reflux, 10 limbs without). Thirty-four limbs (87%) were followed during a median 19 months (range, 1 to 84 months) after stent placement. The cumulative rates of limbs with completely healed ulcers for the two subsets with and without reflux were 67% and 76% at 2.5 years (Fig 5), with no significant difference ($P = .34$ by log-rank test). Only 12 of the 34 ulcer patients (healed 8 and unhealed 4) reported using compression devices, which appears not to have been a major factor in ulcer healing. At 2.5 years, the cumulative overall good or excellent clinical outcomes (grades 2 and 3 as per reporting standards)[14] for patients with and without reflux were similar at 75% and 79% ($P = .31$ by log-rank test) (Fig 6).

DISCUSSION

With IVUS, a newer clinical profile of NIVL has emerged: the disease is dominant but not exclusive to left lower limbs of young women. Clearly, no patient should be excluded from consideration of the syndrome based on age, sex, bilaterality, or involvement of the right side. Leg swelling in older patients is often dismissed as due to cardiac

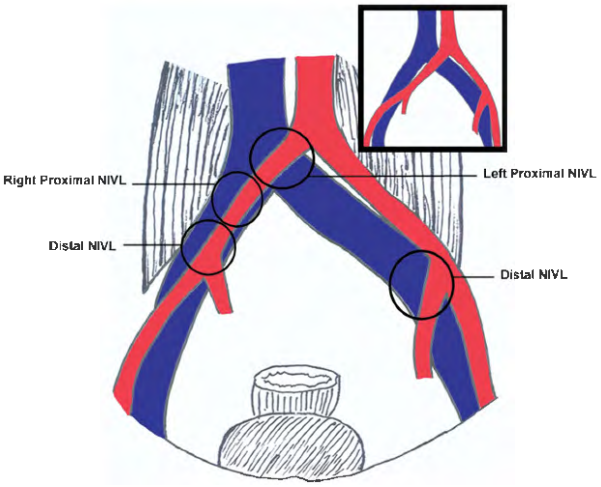

Fig 7. The pathologic anatomy of a nonthrombotic iliac vein lesion *(NIVL)*. The classic left-sided proximal lesion is related to abrupt crossing of the left iliac vein by the right iliac artery. The subsequent course of the right iliac artery is variable (see text). The minority pattern (22%) is shown in the large drawing. Coursing lazily across the vein, the right iliac artery may be related to the proximal or distal NIVL, or both. In the majority pattern (prevalent in 75%, shown in the inset), the right iliac artery crosses the right common iliac vein more abruptly, but lower down at or near the external iliac vein level, inducing distal right NIVL but will not be a factor in proximal right NIVL. The left hypogastric artery crossing may be related to left distal NIVL. The hypogastric veins have been omitted to reduce clutter.

causes, hormonal imbalance, or fluid retention without adequate venous investigation. Clinical benefit and quality-of-life improvement in this age group from a low-risk stent procedure can be impressive. Many in this series were geriatric, and the oldest patient was 90 years old. Some younger patients were symptomatic in their early teens, but stent placement was deferred until the vasculature reached adult size.

The right iliac artery *always* crosses the left common iliac vein abruptly and is related to the classic proximal left NIVL. Subsequent course of the right iliac artery is variable, with variable compression points as detailed by Negus et al.[5] It crosses the right common iliac vein in only 22% (minority pattern) as shown in Fig 7, coursing lazily over a longer length of the vein. The long overlay may be variably responsible for either the proximal or distal NIVL, or both. In 75% (majority pattern), the right iliac artery crosses the right iliac vein more abruptly and at a more distal point over or near the external iliac vein level (Fig 7 inset), in which case, it may induce right distal NIVL but will not be a factor in right proximal NIVL.[5] The left distal lesion may be related to the crossing of the vein by the left hypogastric artery. The right hypogastric artery does *not* cross the iliac vein at all or only partially either in the majority or the minority pattern and therefore does not have a role in right distal NIVLs. Thus, proclivity for NIVLs of all locations, right or left, proximal or distal, exists only in the minority pattern; the majority pattern favors all except the right proximal NIVL. These anatomic variations may explain why proximal NIVLs occur much more frequently on the left side than on the right side, why the left lesion is focal and the right less so, and why the distal NIVL occurs equally on either side.

The poor diagnostic sensitivity of venography was well documented by Negus et al,[5] and venographic data presented here are strikingly similar. Of practical importance is that a third to half of the cases can be missed if frontal projection venograms alone are relied on for diagnosis. Diagnostic sensitivity may be increased by special projections, a cumbersome process that increases radiation exposure (Fig 8).

The frequent absence of venographic collaterals was noted by Negus et al.[5] Collaterals may be absent even in high-grade obstructions.[19] Very little is known about venous collateral development. Collateral development probably requires a higher degree of stenosis than is necessary to generate symptoms of pain and swelling.[22] IVUS has a diagnostic sensitivity of >90% and is indispensable in successful stent placement.[13,15,17,22,23]

The pathogenic role of NIVL in chronic venous disease. The left–right ratio of the clinical syndrome roughly correlates with the left–right distribution of NIVLs, suggesting a connection. In our own practice, we have noticed that the left lower limb may be symptomatic and the right side asymptomatic, even when ambulatory venous pressure is *worse* on the *right* side (unpublished data). The excellent therapeutic response to stent placement indicates that the NIVL contributes in some way to CVD pathology. Of particular interest is the subset with NIVLs with reflux that became symptom–free with stent correction of the NIVL alone, even when the reflux component remained uncorrected. Notably, 67% of stasis ulcers in this subset also healed and remained healed at 2.5 years, ruling out a placebo effect. CVD symptoms, including stasis ulcers, are not due to reflux alone; the NIVL plays a role in ways yet to be understood. Ulcers also occur in NIVLs without reflux, although the incidence is higher with reflux.

The high prevalence and pathologic role of NIVLs in symptomatic CVD patients have to be squared with the frequent prevalence of NIVLs in the asymptomatic general population. The latter fact has raised scepticism that the NIVL is even pathogenic,[9] with the suggestion that it should be viewed as a "normal" anatomic variant. Why do these lesions become symptomatic in some but remain silent in most?

These apparent contradictions can be resolved if the NIVL is viewed as a permissive condition predisposing to the development of CVD. Permissive conditions are pathologies that may remain variably silent until additional insult or pathology is superimposed. Interruption of major venous pathways cannot be considered a "normal variant," only clinically asymptomatic. There is extensive literature on pathologic and iatrogenic major venous interruptions.

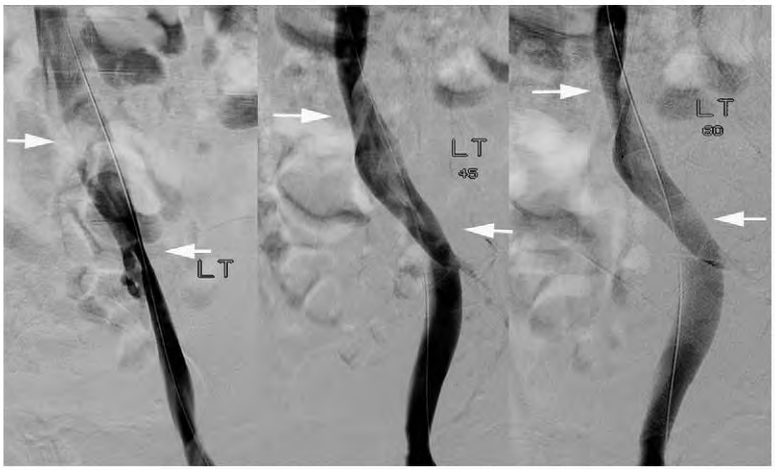

Fig 8. The proximal lesion is coronal and the distal lesion is often sagittal as the hypogastric artery crosses the vein from anterior to the posterior rather than transversely. Note the differential appearance and disappearance of the lesions as the tube is rotated from midline to lateral in the coronal plane: 0° **(Left)**, 45° **(Middle)**, and 60° **(Right)**. The proximal lesion is spiral, often giving a corkscrew appearance.

They are often clinically tolerated,[24,25] but not always.[26,27] Symptom expression would depend on if the interruption is acute or chronic,[28] partial or total,[29,30] peripheral or central, and on the pace and extent of collateralization.[26,31,32] Concomitant reflux or other pathology usually renders the limb symptomatic.[26,31] Hemodynamic abnormalities may be present even in the absence of symptoms.[31,32] Numerous reports have been published of silent congenital or acquired inferior vena cava occlusions discovered incidentally on imaging studies that become symptomatic with the onset of distal thrombosis.[28,33,34]

It is therefore not surprising that many NIVL obstructions remain asymptomatic, because it probably is a slowly progressive condition. Additional insult or pathology such as trauma, cellulitis, distal thrombosis, secondary lymphatic exhaustion,[35] or commonly, reflux, may render the extremity symptomatic. Fluid balance in the limb is on the edge during orthostasis, even in healthy individuals.[36] In the elderly, atherosclerosis of the overlying artery, venosclerosis, decreasing mobility, and leg dependency, or other comorbid conditions predisposing to pedal edema, may be contributory factors in symptom expression.

In others, the precipitating cause for symptoms is obscure. This is in line with numerous other known permissive conditions that may remain variably silent but predispose to secondary pathology and symptoms with additional insult. Some well-known examples include gastroesophageal reflux disease and asthma, ureteric reflux and pyelonephritis, patent foramen ovale and embolic stroke, cricopharyngeal spasm and Zenker's diverticulum, esophageal reflux and cancer, obesity and diabetes, diabetes and neuropathy, middle lobe syndrome and pneumonia, and carotid stenosis and neurologic sequelae. The general principle in these complex pathologies is to treat the permissive condition first, which alone may provide relief, and to prevent recurrence. Correction of secondary pathology may be required only in recalcitrant and advanced cases.

In this series, 75% of limbs with NIVLs and concurrent reflux experienced a good or excellent outcome with stent placement alone, even when the reflux component, severe in many, was uncorrected. These results support the concept that the NIVL plays a permissive role in the genesis of CVD symptoms. It seems highly unlikely that the good outcome could be attributed to enhanced postoperative stocking use, because patients were encouraged to abandon stockings after stent placement. NIVLs are ubiquitous in CVD with severe symptoms, and liberal use of IVUS and stent correction when detected is recommended. Even patients with significant distal reflux benefit, thus avoiding or postponing open reflux corrective procedures, which are not precluded if the stents were to fail later.

When symptoms recur after initial remission following stent placement, our current practice is to perform an IVUS to ensure proper stent function. Often, stent malfunction is found, such as distal migration of the stent with recurrence of the lesion at the iliac-caval junction, missed or incomplete treatment of the distal lesion, or less commonly, in-stent stenoses. When corrected, the patient is usually returned to the status of symptom remission. These beneficial results of reinterventions are not shown in the cumulative curves of the results presented here, because only the results of primary interventions are displayed, and limbs with subsequent reinterventions were censored at the time of symptom recurrence. Valve reconstruction has been required in only a handful of cases (<5%) during the reported observation period for persistent recurrent symptoms.

An alternative explanation for the observations presented here is to consider NIVLs and distal reflux as a continuum in progressive hemodynamic deterioration of

the venous system; symptomatic decompensation occurs when the hemodynamics cross a certain critical threshold. However, no connection between NIVLs and distal reflux has yet been established. Furthermore, the hemodynamics of the respective pathologies are poorly understood, and the relevant metrics even less, to offer tangible support for the latter concept at this time.

AUTHOR CONTRIBUTIONS

Conception and design: SR, PN
Analysis and interpretation: SR, PN
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