

Virchow's triad in "silent" deep vein thrombosis



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ABSTRACT

Objective: While determining the incidence of chronic deep vein thrombosis (DVT) and the hypercoagulation profiles of patients who underwent venous stenting for symptomatic venous insufficiency, we assessed the significance of Virchow's triad in the setting of proximal venous outflow obstruction and DVT.

Methods: Within our registry of 500 patients who underwent venous stenting for proximal venous outflow obstruction between 2013 and 2016, we selected the first 152 consecutive patients who had routine hypercoagulation profile testing performed preoperatively. Statistical analysis was performed using independent *t*-tests, χ^2 tests, and multiple logistic regressions.

Results: By history or intraoperative chronic postphlebotic changes (CPPCs), 77 patients (50.7%) were positive for remote DVT; 51 (33.6%) had intraoperative findings of CPPCs without a history of DVT, 20 (13.2%) had intraoperative CPPCs with a history of DVT, and 6 (3.9%) had a history of DVT without intraoperative findings. The χ^2 tests were significant for increased findings of CPPCs among patients with a history of DVT (81% vs 38%; $P < .01$). The χ^2 tests were also significant for increased rates of intraoperative findings of CPPCs in patients with one or more positive hypercoagulation markers (67% vs 42%; $P < .01$). The most significant predictor for findings of CPPCs or DVT history was the presence of at least one hypercoagulation marker ($n = 148$; odds ratio, 2.41; $P = .022$).

Conclusions: Remote history of DVT and intraoperative findings of CPPCs were prevalent. CPPC findings were found in many patients with no history of DVT. Hypercoagulation markers conferred significant predictive value for DVT. This information may influence our understanding of Virchow's triad and DVT etiology. (*J Vasc Surg: Venous and Lym Dis* 2019;7:640-5.)

Keywords: Chronic venous disease; Venous thromboembolism; Venous insufficiency; Deep vein thrombosis (DVT); Virchow's triad

Thromboembolism in veins has remained a major cause of morbidity and mortality. As many as 900,000 Americans may be affected by venous thromboembolism each year, and anywhere from 60,000 to 100,000 people in the United States die of this condition every year.¹ Virchow's triad describes stasis, hypercoagulable states, and endothelial injury as three important factors that contribute to the initial thrombosis.² Hypercoagulable states have been extensively studied, and the association with thrombosis is well documented. The same

could not be said of stasis and endothelial injury.³ Despite that Virchow's triad is a cornerstone of our understanding of venous thrombosis, the precise nature of the stasis and endothelial injury remains poorly described. As happens occasionally in medicine, further clarification comes from an unexpected source.

For several years, our group has been investigating the placement of stents in the iliac veins for treatment of venous disease in the lower extremities. These vein stent patients usually present with significant, unrelenting edema, and some present with active, debilitating ulceration. In many of these patients, the cause of these symptoms is an obstruction in the iliac veins due to external compression. The most commonly known iliac vein stenosis is May-Thurner syndrome, which is compression of the proximal left common iliac vein by the crossing right common iliac artery above and the lumbar vertebral body below. Compressions also occur elsewhere in the common iliac veins and external iliac veins, but these compressions are less frequent. In our population of patients, we systematically obtained hypercoagulation profiles as part of a study protocol to study the relationship between hypercoagulable states and deep vein thrombosis (DVT). During the stent placement procedure of our patients, the iliac veins of each

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patient were evaluated with both venography and intravascular ultrasound (IVUS). This provided not only the anatomy of the iliac vein but also a way to directly visualize the luminal surface and vessel wall of each iliac vein by IVUS. This study reports the findings of venography and IVUS examination of these patients and how these findings may further elucidate Virchow's triad.

METHODS

The Sinai Vein Stent Registry is an Institutional Review Board-approved database composed of 500 patients who underwent venous stent placement for chronic proximal venous outflow obstruction (PVOO) at the Mount Sinai Hospital in New York City from 2013 to 2016. We retrospectively reviewed the medical records of 152 consecutive patients who underwent iliac vein stent placement for chronic PVOO from October 2013 to March 2015. One notable exclusion criterion was the presence of acute DVT within 90 days before venous stent placement. We divided the study patients into three groups: those with no known history of DVT; patients with a known history of DVT in the past; and those with intraoperative findings of chronic postphlebotic changes (CPPCs) as demonstrated by venography and IVUS with no history or suggestion of previous DVT (ie, those with "silent" DVTs). Angiographic findings designated as CPPCs included diffuse, long-segment stenosis and complete vessel occlusion (Figs 1 and 2). IVUS findings of CPPCs included diffuse stenosis, vessel occlusion, wall thickening, intraluminal filling defects, and absence of an artery or object externally compressing the vein. A



Fig 1. Venogram showing a diffuse stenosis in the left external iliac vein suggestive of a remote deep vein thrombosis (DVT) rather than a stenosis from external compression, which is usually focal.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective cross-sectional study
- **Key Findings:** Of 152 patients who underwent iliac vein stent placement, 51 (33.6%) had intraoperative findings of deep vein thrombosis (DVT) without a known history. Increased rates of intraoperative post-thrombotic changes in patients with one or more positive hypercoagulation markers (67% vs 42%; $P < .01$) were found.
- **Take Home Message:** One-third of the patients undergoing iliac vein stenting had intraoperative findings of DVT without any prior history; hypercoagulation markers predicted previous DVT.

preoperative hypercoagulable profile obtained in each patient included antithrombin III antigen, homocysteine levels, anticardiolipin immunoglobulin M or G, factor V Leiden, dilute Russell viper venom time, lupus anticoagulant, β_2 -glycoprotein antibody (immunoglobulin A, G, or M), antinuclear antibody, prothrombin G20210A mutation, and protein C and protein S function. Preoperative demographic and comorbidity data were analyzed using independent *t*-tests, Fisher exact tests, and χ^2 tests, and focused hypercoagulation profiles consisting of 11 indicators of hypercoagulation were used to perform a multiple logistic regression to identify potential predictors of DVT. Postoperatively, patients were prescribed rivaroxaban 10 mg once daily and subsequently transitioned to aspirin 81 mg at either 3 or 6 months as prophylaxis against DVT. The decision is based on whether the stenosis is pure compression or compression and post-thrombotic stenosis by intraoperative findings.

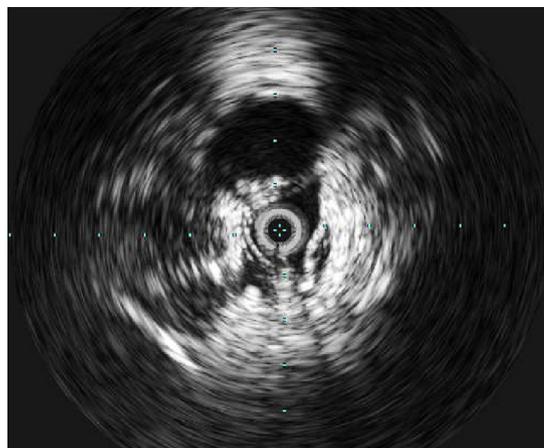


Fig 2. The intravascular ultrasound (IVUS) catheter in this image is in the external iliac vein, which is severely stenotic. The external iliac artery is adjacent to the vein, but it is not the cause of the stenosis.

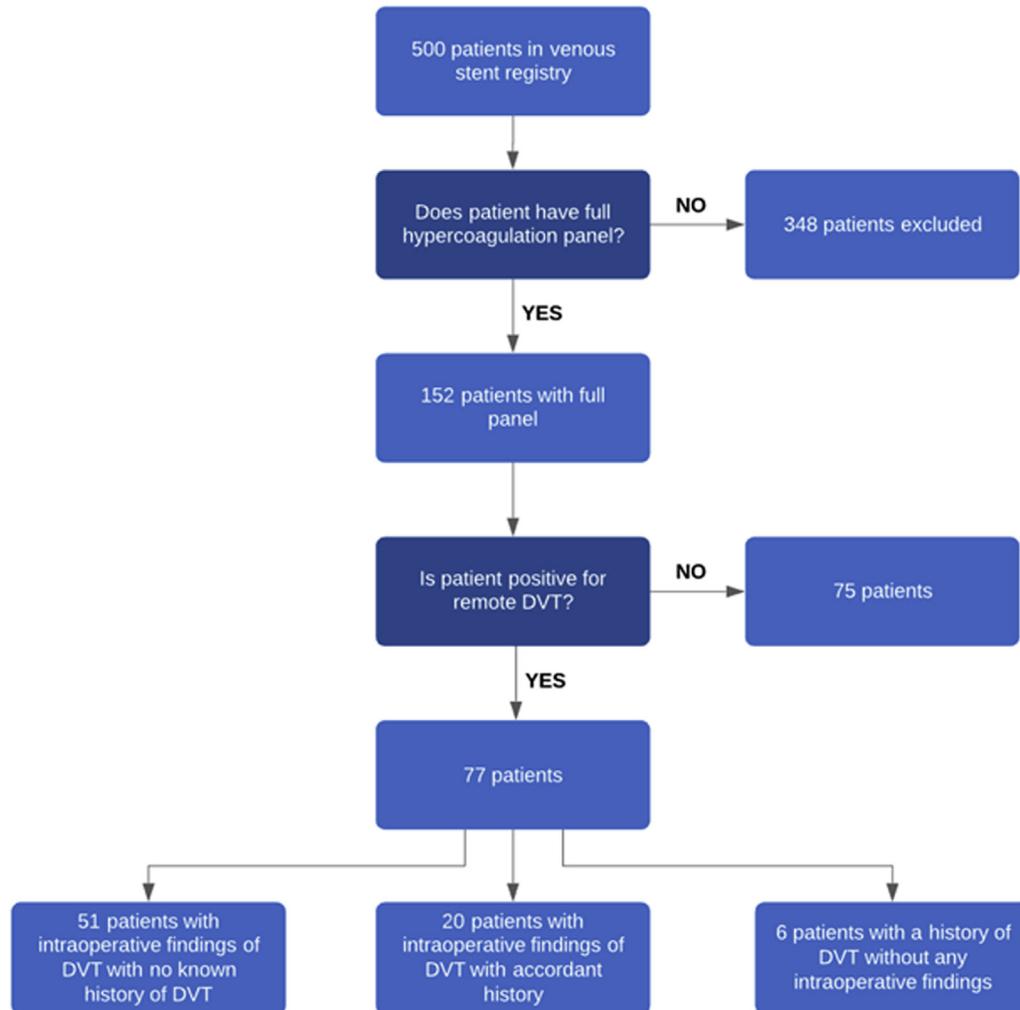


Fig 3. Patient flow chart. *DVT*, Deep vein thrombosis.

RESULTS

Of the 152 patients who underwent iliac vein stent placement, 77 (50.7%) were positive for remote DVT by either history or intraoperative findings of CPPCs (diffuse long-segment stenosis, vessel occlusion, or intraluminal filling defects by venography or IVUS; Fig 3). In this group positive for intraoperative findings or history of DVT, there were no statistically significant differences in terms of patients' clinical scenario (such as patients presenting with varicose veins and awaiting endovenous laser ablation), patients presenting with persistent symptoms after endovenous laser ablation, or patients presenting with edema and other venous symptoms in comparison to those without a history of DVT or intraoperative findings of CPPCs (Table I). Of this cohort with intraoperative evidence of previous DVT, 51 patients (33.6%) had intraoperative findings of CPPCs without a known history of DVT, 20 (13.2%) had intraoperative chronic phlebitic findings with a known history of DVT, and 6 (3.9%) had a known history of DVT with no intraoperative findings of the condition.

In our study, 148 patients (98%) presented with edema, and 110 patients (72%) presented with varicose veins (there were no significant differences between the DVT group and non-DVT group). However, 20 patients (26%) with intraoperative findings of DVT or a history of DVT presented with active ulceration, whereas 9 patients (12%) without any findings of DVT or history of DVT presented with this same complaint.

There were no significant differences between patients with intraoperative evidence or history of DVT and those patients without any DVT in terms of average number of follow-up appointments (four) or percentage of patients attending periodic follow-up appointments (Table II). Almost all patients in the study (151) attended at least one follow-up appointment (99%), and 148 patients (97%) attended their first follow-up appointment (at 3 months after the procedure). In addition, the length of time from venous stenting to most recent follow-up appointment was not significantly different between the two groups (531 days in the DVT group vs 502 days in the group without DVT; $P > .05$). Rates of reoperation

Table I. Patients' demographics

Total patients	152
Patients with DVT (intraoperative findings or history)	77
Patients without any DVT	75
Age, years	62.4 (13.8)
Patients with DVT	62.7 (12.6)
Patients without DVT	62.2 (15.0)
Sex, female:male	88:64 (58% female)
Patients with DVT	43:34 (56% female)
Patients without DVT	45:30 (60% female)
Presenting characteristics	
Patients with DVT	
Presenting with edema	76 (99)
Presenting with active ulceration	20 (26)
Presenting with varicose veins	55 (71)
Patients without DVT	
Presenting with edema	72 (96)
Presenting with active ulceration	9 (12)
Presenting with varicose veins	55 (73)
DVT, Deep vein thrombosis. Categorical variables are presented as number (%). Continuous variables are presented as mean (standard deviation). Some patients fulfilled criteria for more than one clinical scenario.	

(ie, a second procedure with re-entry into the iliac vein) were also not statistically different between these two groups (16 patients [21%] in the DVT group vs 15 patients [20%] in the group without DVT; $P > .05$).

Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) classification of the patients with a history of DVT or intraoperative findings of DVT differed from that of the patients without any known DVT (Table III). Of

Table II. Outcomes of stenting procedures

	Patients with DVT (n = 77), No. (%)	Patients without DVT (n = 75), No. (%)
No. of follow-up appointments attended since operation (average)	4	4
Patients attending follow-up at		
30 days	74 (96)	74 (99)
90 days	67 (87)	69 (91)
6 months	66 (86)	62 (81)
1 year	54 (70)	56 (75)
>1 year	49 (64)	41 (55)
Any follow-up whatsoever	76 (99)	75 (100)
Time from operation to most recent follow-up, days, average	531	502
Patients having reoperations	16 (21)	15 (20)
DVT, Deep vein thrombosis.		

the patients with DVT, 42 patients were CEAP class 4 or higher (55%), whereas 24 patients without any evidence of DVT were CEAP class 4 or higher (32%); 20 patients with evidence of DVT were CEAP class 6 compared with 9 patients without any evidence of DVT (20 vs 9 patients; $P = .0383$). In addition, in both groups, the most common CEAP class was CEAP class 3; more than half of patients without any evidence of DVT were CEAP class 3, whereas this figure was lower for patients with evidence of DVT (34 vs 50 patients; $P = .0059$).

The χ^2 tests were significant for increased intraoperative findings of CPPCs among patients with a history of DVT (81% vs 38%; $P < .01$). The χ^2 tests were also significant for increased rates of intraoperative findings of CPPCs in patients with one or more positive hypercoagulation markers (67% vs 42%; $P < .01$). However, individual and smaller groupings of these hypercoagulation markers did not significantly correlate with increased rates of intraoperative findings of CPPCs. The most significant predictor for intraoperative findings of CPPCs or DVT history was the presence of at least one hypercoagulation marker ($n = 148$; odds ratio, 2.41; $P = .022$).

DISCUSSION

Among our patients, we observed a significant and unexpected prevalence of patients with silent DVTs. We found that many patients undergoing venous stent placement for PVOO were noted to have thromboses of which they were totally unaware; 51 of our patients fit this profile, and another 26 had a known history of DVT (regardless of intraoperative findings). The indications for stent placement in this population were often due to complications and venous stasis associated with May-Thurner syndrome. This condition arises because of the extrinsic impedance and entrapment of the common iliac vein due to obstruction by the overlying common iliac artery, making it a predisposing factor to the manifestations of venous disease, including skin changes, edema, lower extremity pain, ulceration, and myriad other symptoms. The relationship between May-Thurner syndrome and symptoms is not entirely

Table III. Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) classifications

CEAP class	Patients with DVT (n = 77), No. (%)	Patients without DVT (n = 75), No. (%)	P value (<.05)
1	0	0	—
2	1 (1)	1 (1)	NS
3	34 (44)	50 (67)	.0059
4	20 (26)	14 (19)	NS
5	2 (3)	1 (1)	NS
6	20 (26)	9 (12)	.0383
DVT, Deep vein thrombosis; NS, not significant.			

clear as the condition may be asymptomatic. Whereas May-Thurner syndrome is thought to be uncommon, it has been suggested that the condition is underestimated in the general population.⁴ May-Thurner syndrome is likely to result in venous stasis, and this phenomenon probably contributes to the incidence of DVT seen among our patients.

As many as 900,000 Americans each year are afflicted by a DVT, of whom around 60,000 to 100,000 die of venous thromboembolism. Alarming, around 50% of those who develop a DVT every year are clinically silent, and a patient's first symptoms of a DVT may be a fatal pulmonary embolism.⁵ Thus, it is of utmost importance to successfully recognize and diagnose DVT. Our findings confirm that many patients with DVT have no knowledge of their condition. Many of our patients with no symptoms of DVT were found to have evidence of a remote DVT during surgery, and we must be cognizant that many patients have such silent DVTs. Our study determined that the presence of at least one of the 11 principal hypercoagulation markers conferred significant predictive value for the presence of DVT in this population of patients, and this relationship deserves further investigation in the future. Recognizing these markers in the clinical setting may aid in prevention and the improved management of patients undergoing venous stenting for PVOO, and it is important that practitioners be mindful of the prevalence of silent DVTs.

The hypercoagulation markers we measured conferred significant predictive value for DVT, and our findings confirm the association of hypercoagulable states with DVT. Clinical judgment was used in determining whether a particular patient received this hypercoagulation panel as well as which tests were performed, and thus selection bias may affect the study population. Nonetheless, our study demonstrated that these factors have an impact on DVT and intraoperative findings of DVT. Whereas complete understanding of the mechanisms is unknown, the information ascertained by our study may aid in management of DVT, PVOO, and patients undergoing vein stent placement for PVOO. Whereas no individual markers conferred significant predictive value for DVT, future efforts should be made to assess a smaller pool of such markers with a larger population of patients.

The Virchow's triad postulates that a dynamic interplay between stasis, hypercoagulability, and endothelial injury directly contributes to venous thrombosis. This model is often cited, but with the exception of hypercoagulable states, it has not been confirmed. Although hypercoagulable states within Virchow's triad have been extensively studied, less attention for literature supports the other two components of the triad. Our work uses our understanding of the multifactorial nature of venous thrombosis to better characterize this relationship and to assess the associations between stasis, as

manifested most often by external compression, and states of hypercoagulability, as measured by aberrations in markers of hypercoagulation. The most well known of such compressions is May-Thurner syndrome, in which the proximal left common iliac vein is externally pressed by the right common iliac artery. In our population of patients, May-Thurner syndrome probably acts as "stasis," composing one foundation of Virchow's triad. May-Thurner syndrome, which is often an unrecognized cause of stasis, may be treated with the placement of a stent across the point of vascular stenosis in symptomatic patients. During vein stenting, the iliac veins are imaged with contrast enhancement as in venography but also with IVUS, an imaging modality that allowed us to visualize the inside of blood vessels and to assess for CPPCs associated with venous thrombosis.

CONCLUSIONS

More than 50% of our patients in this study were found to have a prior history of DVT or intraoperative findings suggestive of CPPCs. Our findings corroborated the previously described incidence of undiagnosed DVT as many of the DVTs we encountered were clinically silent to the patient.⁶⁻⁹ We were surprised to discover that more than one-third of our patients undergoing stent placement for the treatment of PVOO were found to have intraoperative findings of DVT without any prior history of the condition. The impact of the hypercoagulation markers that we have assessed ought to be elucidated in the future. Our current findings offer a novel lens for interpreting Virchow's triad and the application of venous stasis, hypercoagulable states, and endothelial damage in understanding the etiology of DVT and hold clinical implications for the management of patients undergoing venous stent placement in the setting of PVOO.

AUTHOR CONTRIBUTIONS

Conception and design: JL, CP, SS, SC, EC, AA, MM, PF, WT
 Analysis and interpretation: JL, CP, SS, SC, WT
 Data collection: JL, CP, SS, SC, WT
 Writing the article: JL, CP, SS, SC, WT
 Critical revision of the article: JL, CP, SS, SC, EC, AA, MM, PF, WT
 Final approval of the article: JL, CP, SS, SC, EC, AA, MM, PF, WT
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 Overall responsibility: WT

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