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Qualitative Slow Blood Flow in Lower Extremity Deep Veins on Doppler Ultrasound: Quantitative Assessment and a Preliminary Evaluation of Correlation with Subsequent DVT Development in a Tertiary Care Oncology Center

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Abstract

Objectives—To determine whether qualitative sonographic appearance of slow deep venous flow in the lower extremities correlates with quantitative slow flow and an increased risk of deep venous thrombosis (DVT) in oncology patients.

Materials and Methods—In this IRB-approved retrospective study, we reviewed lower extremity venous Doppler ultrasounds for 975 consecutive patients: 482 with slow flow and 493 with normal flow. The subjective slow venous flow and absence of initial DVT were confirmed by two radiologists. Peak velocities were recorded at three levels. Each patient was followed for DVT development.

The associations between DVT and the presence of slow venous flow were examined using Fisher exact test; the two-sample *t* test was used for peak velocity and DVT group comparisons. The optimal cutoff peak velocity to correlate with the radiologists' perceived slow flow was determined by Youden's index.

Results—DVT development in the slow flow group (21/482, 4.36%) was almost doubled compared to patients with normal flow (11/493, 2.23%) (P=0.0456). Measured peak venous velocities were lower in the slow venous flow group (P<0.001). Patients with subsequent DVT did not have a significant difference in venous velocities compared with their respective patient group.

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The sum of three venous level velocities resulted in the best cutoff to dichotomize groups into normal versus slow venous flow.

Conclusions—Qualitative slow venous flow in the lower extremities on Doppler ultrasound accurately correlates with quantitatively slower flow and preliminary evaluation suggests an associated mild, increased rate of subsequent DVT development in oncology patients.

Keywords

DVT; VTE; venous flow; venous thrombosis; ultrasound

INTRODUCTION

The Virchow triad classically consists of three factors leading to venous thrombosis: stasis, vessel wall injury, and hypercoagulable states. [1] Although our understanding of venous thrombosis pathophysiology has increased, more focus has been given to diagnostic and treatment pathways with the development of patient risk stratification algorithms such as the Wells score or Hamilton score and new medical therapies for venous thrombosis. [2,3] The clinical and research focus on deep venous thrombosis (DVT) has been driven by its associated significant morbidity, mortality, and resource utilization across worldwide populations [4]; specifically, DVT from the lower extremities accounts for approximately 80% of venous thromboembolism (VTE) with an estimated VTE incidence of 900,000 per year. [5] Of these cases, 20% are attributed to malignancy. [6] This increased risk is elevated further in patients receiving chemotherapy, more so than the risk associated with congestive heart failure or the general increased risk associated with hospitalization. [7, 8] Numerous other risk factors for DVT have been identified such as prolonged intensive care unit admission, immobility, history of prior DVT/VTE, infection and the presence of a central venous catheter. [5, 9, 10]

Despite the important progress that has been made in understanding DVT, there are many aspects of DVT that require further evaluation. Slow venous flow, observed on Doppler ultrasound, is one such area needing further assessment, specifically as it relates to DVT. The concept of “sluggish” venous flow, or “stasis,” has been recognized for centuries but has been studied in only a few patient groups, with limited scientific rigor.[11] A few previous studies have directly evaluated slow venous flow, and others have indirectly assessed patients at risk with presumed or confirmed venous stasis. Direct evaluations include work by Lozano et al.[12] who assessed 218 patients in the immediate postoperative period after ipsilateral inguinal hernioplasty with mesh placement. This study demonstrated short-term slowing of deep venous flow without increased incidence of VTE and near normalization of flow 7 days thereafter. [12] An even shorter duration of slow venous flow was shown during intraperitoneal insufflation for laparoscopy, without evidence of increased rate of DVT. [13] However, medical practice commonly attributes increased risk of DVT to venous stasis or factors presumed to decrease deep venous flow. For example, multiple authors have evaluated slow venous flow in the surgical setting with mention of increased associated risk of DVT, but they have provided only limited supporting evidence. [14-16] Indirect evaluations of venous stasis include work by Scurr et al.[17] who evaluated an otherwise normal population of airline passengers and showed increased incidence of DVT.

The potential correlation of slow venous flow on ultrasound with increased risk of subsequent DVT formation would have significant implications for patient prognosis and management. Therefore, herein, we evaluate whether the qualitative sonographic appearance of slow deep venous flow in the lower extremities correlates with quantitative measures of slow flow and whether there is an increased risk of subsequent DVT in oncology patients.

To our knowledge, this is the first such evaluation of a general oncologic population and the largest study to evaluate slow deep venous flow identified sonographically.

MATERIALS AND METHODS

In this Institutional Review Board-approved and Health Insurance Portability and Accountability Act compliant retrospective study, two groups of lower extremity venous Doppler ultrasounds were reviewed by two radiologists: those of consecutive patients *with* reported slow or sluggish venous flow, who were identified for analysis on the basis of a search of radiology reports between January 1, 2008, and January 1, 2015, and a group of consecutive patients *without* reported abnormal venous flow (normal flow group) between February 1, 2013 and November 31, 2014.

All examinations were performed in our ACR accredited department, most examinations by sonographers certified in vascular registry of the RDMS (Registry of Diagnostic Medical Sonography), under the supervision of the senior author (over 30 years ultrasound experience). Equipment utilized was either Philips iU22 (Philips Healthcare, Bothell, Washington) or Logiq E9 (General Electric, Milwaukee, WI). Most were performed using linear transducers, 9-12 mHz. A small number required curved array transducers, 2-5 MHz, for limited sections of the femoral veins. When presets on the machines were judged to be inadequate by the sonographer, individual gain and focal zone adjustments were made specifically for that patient. Real-time cine loop images are standard in our department in equivocal cases and were reviewed for this study; this enabled the differentiation of sonographic artifact from slow flow in all cases.

The presence or absence of qualitative slow venous flow and absence of initial or recent DVT (within 30 days), as per the official radiology report and clinic notes, were confirmed with reevaluation by two radiologists (V.A., a senior radiology resident, and C.J., a board certified radiologist with an abdominal imaging fellowship); potential discrepancies were addressed through consensus reevaluation (<1% of all cases reviewed) without any patients being excluded from either group. *Slow venous flow without thrombus* was qualitatively defined as amorphous echogenicity, greater than that of the adjacent artery, throughout the fully compressible venous lumen (Figure 1). In many cases, cine imaging had been performed, but this was not used as a standard in our study given that cine imaging was not performed in *all* cases. Per departmental protocol, in addition to the common femoral, femoral and popliteal levels, the deep calf veins were assessed whenever focal symptoms were attributed to a region below the knee.

Peak venous flow velocities were recorded at the common femoral, femoral and popliteal levels based on standard spectral waveforms.

Each patient had clinical and/or sonographic follow-up with the number of days between incident U/S examination and most recent encounter recorded.

Medical records were reviewed retrospectively to identify, at the time of the incident ultrasound examination, whether the patient was an inpatient or outpatient. Patients' age, gender, acute pathology, mobility status, significant past medical history, medications, primary tumor histology, history of chemotherapy within 30 days and cross-sectional imaging within 30 days (before or after) were recorded. Reports and images from any available cross-sectional examinations of the abdomen/pelvis were reviewed for the possible presence of a lesion (e.g. tumor, lymphadenopathy, stenosis) that could obstruct venous flow. D-dimer level and, if medications included warfarin, international normalized ratio (INR) were recorded if obtained within 7 days of the ultrasound (Tables 1a and 1b).

The descriptive statistics for continuous clinical factors have been summarized and compared between DVT and non-DVT groups by using a two-sample *t* test (Table 2). The associations between DVT and other factors such as the presence of slow venous flow or dichotomized peak velocity were examined using Fisher's exact test, as was applied for comparison of all categorical variables. A two-sample *t* test or Wilcoxon rank sum test was applied for comparison of continuous variables. The *P* values were adjusted for multiple testing by using the Benjamini-Hochberg procedure. [18] Logistic regression was applied to determine whether age and gender correlate with the presence of slow flow. A two-sample *t* test was used for peak velocity comparison of (1) slow flow versus normal groups and (2) DVT versus non-DVT. The optimal cutoff point for peak velocity was determined by Youden's index. [19, 20]

All of the analyses were conducted using R statistical software version 3.1.2 with packages pROC and OptimalCutpoints. A *P* value of 0.05 or smaller was considered statistically significant.

RESULTS

The study group consisted of 482 consecutive patients *with* reported slow or sluggish venous flow (46% were bilateral exams) and 493 consecutive patients *without* reported abnormal venous flow (normal flow)(55% were bilateral exams) for a total of 975 patients whose venous flow was assessed by ultrasonography. The top four indications for the incident ultrasound were edema, pain, shortness of breath and pulmonary embolism for both the normal and slow flow groups accounting for 89% and 78% of all indications, respectively. No significant difference in age was present between the two groups. More men than women had slow venous flow (odds ratio 1.5, 95% confidence interval [CI] 1.163-1.937, P=0.002). No correlation was found between DVT and patient age, primary tumor site, tumor histopathology or gender.

The increased rate of subsequent DVT development in the slow venous flow group (21/482, 4.36%) compared with the normal flow group (11/493, 2.23%) was statistically significant (P=0.0456). When assessing within each flow group, no significant difference in peak velocities was found between patients that did or did not develop subsequent DVT. For

example, within the group already known to have slow flow, there was no further difference in velocities *within* the group to indicate who ultimately developed subsequent DVT.

Patients within the normal and slow flow groups were followed up to an average of 410 days from incident U/S (median 266 days) and 439 days (median 161 days), respectively. 68 out of 493 in the normal flow group and 75 out of 482 in the slow flow group had a follow-up lower extremity ultrasound. The remainder of the patients underwent at least one standard follow-visit including history and physical examination, but most patients were seen multiple times during this follow-up period. 28 patients in the control group and 11 patients in the slow flow group had a last documented encounter of less than 30 days from incident U/S without recorded death. 24 patients and 34 patients died within 7 days of incident U/S in the slow flow and normal flow groups, respectively; none of these deaths were known to be attributed to PE/DVT. 236 patients and 196 patients died within 6 months of the incident U/S from the control and slow flow groups, respectively.

In the slow flow group, 79 patients had recent cross-sectional imaging with a finding to reasonably explain slow venous flow such as compressing/infiltrating mass or stenosis. Of note, using this same criteria, 44 patients with such findings were identified in the normal flow group. Pertinent, recent cross-sectional imaging was not present in 100 patients in the slow flow group or 178 patients in the normal flow group.

Radiologist qualitative identification of slow venous flow was confirmed quantitatively; the measured peak venous velocities were significantly lower in the slow venous flow group at each assessed venous level ($P<0.001$) by an average of 9, 5 and 6 cm/s at the common femoral, femoral, and popliteal levels, respectively. The sum of the three venous level velocities resulted in the best cutoff to dichotomize groups into normal versus slow venous using a value of 42 cm/s in the left leg and 45 cm/s in the right leg (Table 3 and 4). This dichotomized value, however, did not correlate with a statistical difference in DVT rate.

DISCUSSION

Venous stasis is commonly considered a risk factor for DVT yet this association remains underevaluated in many patient groups. [10] Our study was a preliminary assessment of oncology patients in a tertiary care center who had documented slow venous flow in the lower extremities on ultrasound without initial DVT. The qualitative identification of slow venous flow in the lower extremities correlated with a statistically significant increased rate of subsequent DVT development ($P=0.0456$). To our knowledge, this is the first study in the evaluation of slow venous flow by ultrasound as it relates to subsequent DVT development in oncology patients.

While the concept of *stasis* leading to venous thrombosis has been described for centuries, there is limited literature on objectively measured slow deep venous flow and its potential correlation with DVT rates. In addition to our demonstration of a statistically significant increased rate of subsequent DVT development in the slow venous flow group, there is further support of our data and this concept through the assessment of individual patients in the slow flow group that developed DVT (Table 4). Interestingly, in cases of subsequent

DVT development where a baseline bilateral exam was performed (N=6) and unilateral DVT developed (N=5), it most often developed in the leg with slower flow (Table 4). In 14 out of 15 cases with unilateral baseline exam, the subsequent DVT developed ipsilateral to the initially symptomatic leg that underwent sonographic evaluation. This later case is confounded by only having a unilateral baseline U/S exam, but this information may be useful in the development of future management algorithms.

The results of our study suggest that implementation of increased imaging surveillance for patients with slow deep venous flow might be reasonable to consider. However, importantly, we observed a wide variation in time to DVT development in both the slow and normal venous flow groups (Table 2); until further studies are performed, the utility of increased medical surveillance is of interest but is uncertain especially as it pertains to various patient groups based on cancer diagnosis, etc.

As slow deep venous flow becomes of more interest in research and clinical practice, identification on ultrasound and diagnostic reporting should increase. Empirically, based on our experience, there is limited reporting of slow venous flow on routine Doppler exams performed for DVT evaluation. Perhaps some of this underreporting is related to the undefined nature of slow venous flow. Our study confirmed that the radiologist's qualitative identification of slow venous flow is accurate when compared to quantitative spectral waveform measurements; importantly, this *qualitative* approach provided dichotomization of patients into clinically significant groups of slow and normal venous flow that were associated with different DVT rates. Whereas the best area under the curve (AUC) was achieved when using the average of the three venous level velocities (14.5 cm/s average using both right and left leg data), the *quantitative* dichotomization did not reach statistical significance with respect to DVT rates. Given the qualitative diagnostic results, it is likely that a larger sample size would result in a statistically significant quantitative measure to stratify patients.

Our study showed a higher percentage of men in the slow deep venous flow group than in the normal flow group; although selection bias may account for this, it is noted that the literature reports that the age-standardized incidence of first-time venous thromboembolism is slightly higher in men. [21] In addition, it was noted that the slow flow group that developed subsequent DVT (n = 21) contained a higher number of male patients; however, this group also had more patients who had received chemotherapy within 30 days of DVT identification, those with positive CT scans, and patients who had undergone recent surgery (within 2 weeks). While in our study these factors were not statistically significant, elucidation of these potential relationships would be of interest and likely useful.

Limitations of this study include its retrospective design. The potential for selection bias was partially addressed by formulating our venous flow groups using consecutive patients. However, our potential slow venous flow group was created by a search of the radiology information reporting system for reports indicating slow venous flow. With this method, cases of slow flow would be missed if not mentioned in the report. Second, our standard lower extremity venous Doppler ultrasound protocol evaluated the common femoral, femoral, and popliteal levels; the deep calf veins were assessed only when focal signs or

symptoms were present below the knee. Therefore, asymptomatic distal DVT could be missed on our review of each baseline and follow-up ultrasound examination. In addition, although patients received clinical follow-up, it was varied in time course and many did not undergo sonographic follow-up. Nevertheless, given the typical close follow-up for our oncologic patient population, it would be unlikely that a clinically significant DVT would remain undiagnosed.

Although this study did assess various potential confounding variables, the small population size of patients with subsequent DVT formation limited evaluation. Importantly, the groups of normal versus slow deep venous flow were remarkably similar suggesting them to be reliable groups for comparison. Specifically, there were no significant differences in important categories such as therapeutic or prophylactic use of anticoagulation (Tables 1a, 1b and 2). For this correlation to be further tested, each unique patient scenario including information such as tumor stage requires identification; there also needs to be control of more variables such as duration of slow venous flow in a prospective manner with a larger sample size. It would be interesting and important to further determine the rate and timing of DVT formation with adjustment for these other factors.

In conclusion, the underlying pathophysiology of slow venous flow in the lower extremities and DVT formation is multifactorial. Our study demonstrates that qualitative identification of slow venous flow is accurate and preliminary evaluation suggests that the presence of slow venous flow in the lower extremity deep veins indicates a small but increased risk of subsequent DVT development. Although further investigation is needed, it would be reasonable for these patients to be more closely monitored clinically and with a lower threshold for follow-up with venous Doppler ultrasound.

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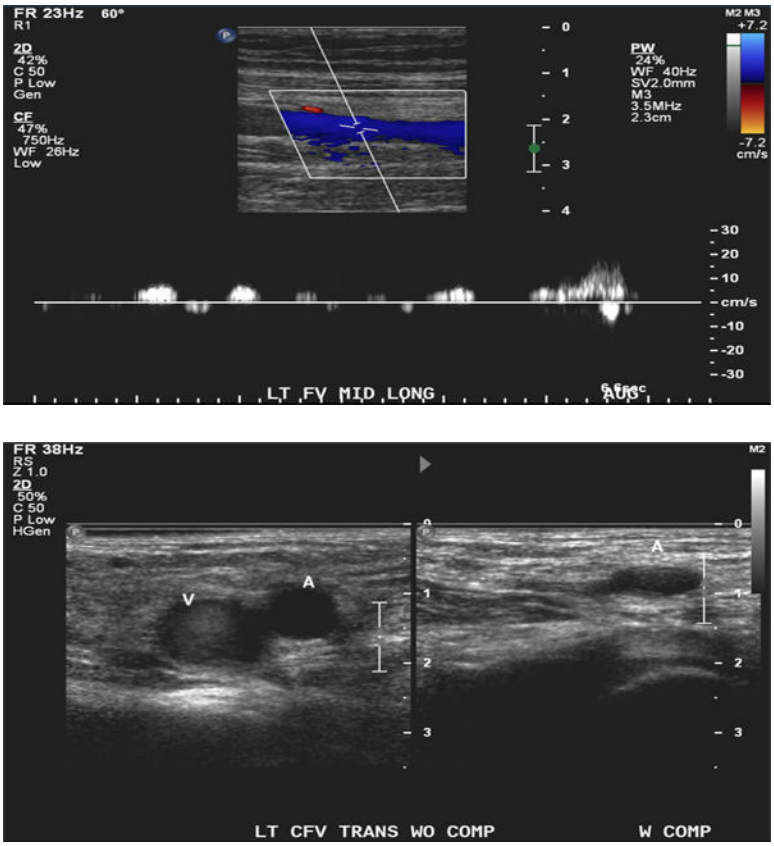

Figure 1.

Example of slow venous flow: echogenicity within the left common femoral vein associated with compressibility and demonstrable slow flow on spectral waveform analysis of the left femoral vein.

Table 1a

Normal Versus Slow Lower Extremity Deep Venous Flow: Patient Characteristics.

	Slow Venous Flow	Normal Venous Flow	*P*-Value‡
Total Patients	482	493	
Male/Female	270/212	231/262	0.0624
Inpatient/Outpatient	156/326	194/299	0.0862
Average age (years)	56	58	0.0862
Elevated D-dimer	106 (119 patients measured)	130 (141 patients measured)	0.6613
Chemo within 30 days	232	208	0.1328
#No. using OCPs	2	2	0.6613
Aspirin ^	59 (16)	75 (21)	0.2791
Clopidogrel	16	12	0.5287
Enoxaparin/heparin ^	56 (135)	38 (114)	0.0862
Warfarin	32	15	0.0682
Rivaroxaban	8	3	0.2268
Dabigatran	2	0	0.3173
Positive CT *	79/384	44/309	0.0862

Note. —

‡Adjusted for false positive rate of multiple testing.

*Positive CT defined as any finding such external compression or stenosis that could potentially explain slow venous flow in the lower extremities.

^Full dose (Prophylactic dose). OCP=oral contraceptive pill.

Table 1b

Cancer Diagnosis Frequencies for the Normal and Slow Deep Venous Flow Groups.

	Slow Venous Flow	Normal Venous Flow
Total Patients	482	493
Leukemia/Lymphoma	48	83
Lung	46	32
Gynecologic	32	38
Colon	32	26
Breast	29	41
Brain	26	26
Prostate	25	17
RCC	25	9
Pancreas	23	15
Melanoma	22	19
Multiple Myeloma	18	22
Sarcoma	12	14
Urothelial	10	12

Note. — Diagnoses shown above represent any category of tumor that was seen in at least 10 patients in either group. RCC=Renal Cell Carcinoma.

Table 2

Normal Versus Slow Deep Venous Flow Group Characteristics for Patients with Subsequent DVT Development.

	Slow Venous Flow (+DVT Group)	Normal Venous Flow (+DVT Group)
Total Patients	21	11
Male/Female	14/7	5/6
Inpatient/Outpatient	5/16	6/5
Average age (years)	54	60
Elevated D-dimer	5/6	2/2
Chemo within 30 days	14	7
#No. using OCPs	0	0
Aspirin ^	3 (3)	1 (1)
Clopidogrel	1	1
Enoxaparin/heparin ^	1 (4)	1 (1)
Warfarin	1	1
Rivaroxaban	1	0
Dabigatran	0	0
Recent Surgery	4	1
Remote history of DVT	1	3
Positive CT *	5/10	1/10
Days to DVT	Median 121 days Avg 212.3 days	Median 60 days Avg 102.6 days
Proximal:Distal DVT	18:3	7:4

Note.—No statistically significant difference between categories.

* Positive CT defined as any finding such external compression or stenosis that could potentially explain slow venous flow in the lower extremities.

^ Full dose (Prophylactic dose).

OCP=oral contraceptive pill.

Table 3

Statistical Evaluation of Velocity Correlation with Qualitative Slow Venous Flow.

	Left Leg				Right Leg			
	CFV	Fem V	Pop V	Sum	CFV	Fem V	Pop V	Sum
Cutoff velocity cm/s	23	12	12	42	17	12	12	45
Sensitivity	0.495	0.736	0.682	0.757	0.802	0.688	0.679	0.668
Specificity	0.838	0.739	0.819	0.746	0.587	0.712	0.805	0.79
PPV	0.138	0.129	0.165	0.136	0.093	0.112	0.155	0.143
NPV	0.969	0.982	0.98	0.983	0.983	0.977	0.979	0.978
AUC (95% CI)	0.737 (0.701, 0.773)	0.777 (0.743, 0.81)	0.789 (0.756, 0.822)	0.814 (0.783, 0.845)	0.752 (0.715, 0.79)	0.735 (0.698, 0.772)	0.772 (0.737, 0.808)	0.793 (0.758, 0.827)

Note.— CFV = common femoral vein, Fem V = femoral vein, Pop V = popliteal vein, PPV = positive predictive value, NPV = negative predictive value, AUC = area under the curve, CI = confidence interval.

Table 4

Six Patients from the Slow Venous Flow Group with Initial Bilateral Lower Extremity U/S Exam and Subsequent DVT Development: Left Leg Versus Right Leg Peak Venous Velocities.

	Patients					
	1	2	3	4	5	6
Peak Velocity CFV (cm/s) L Leg:R Leg	8:13	45:40	14:24	12:22	22:18	14:12
Peak Velocity FV (cm/s) L Leg:R Leg	8:10	9:8	9:12	8:11	11:14	5:5
Peak Velocity Pop V (cm/s) L Leg:R Leg	10:10	5:8	9:8	8:11	12:16	7:6
Subsequent DVT Location	L CFV, FV, Pop V	L Peroneal (Calf)	L Peroneal (Calf)	L Peroneal (Calf)	Bilateral FV, Pop V	R FV and Pop V

Note.—U/S = ultrasound, DVT = deep venous thrombosis, CFV = Common femoral vein, Fem V = femoral vein, Pop V = popliteal vein. In cases of positive DVT where a baseline bilateral U/S exam was done and unilateral DVT developed, it developed in the leg with slower flow in 3 out of 4 patients; one case had bilateral DVT and another had symmetrically slow flow in each leg. In cases where the baseline was unilateral (not shown above), the subsequent DVT was always documented on that same side.