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Assessment of residual thrombus after venous thrombolytic regimens

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Background: **We noticed substantial residual thrombus on intravascular ultrasound (IVUS) in many limbs despite restoration of flow after thrombolysis. Since thrombus burden has been tied to post-thrombotic syndrome (PTS), the frequency and extent of residual thrombus after thrombolysis is important. We present such an analysis below.**

Methods: **Sixty-seven limbs underwent (median age, 57; range, 24-83) pharmacomechanical thrombectomy (PMT) after deep venous thrombosis (DVT) (35 limbs) or iliac vein stent thrombosis (32 limbs). Assessment after PMT included venography and IVUS. If flow was not established or residual thrombus was present on IVUS examination, follow-up catheter-directed thrombolysis (CDT) up to 3 days was used to clear the thrombus.**

Results: **PMT was successful in establishing flow across occluded segments in 82%, but complete lysis per IVUS was achieved in only 9% with residual thrombus present in 91% (18% occlusive) of treated limbs. Follow-up CDT was feasible in 48 limbs. This resulted in establishment of inline flow in nine additional limbs; complete thrombus clearance per IVUS was achieved in 15 others (many with prior inline flow with thrombus). Overall, 96% of limbs were patent, but as many as 69% of limbs had residual thrombus after treatment with one or both lytic regimens. There was significantly more complete clot clearance ($P < .04$) in virgin DVT compared with thrombosis in stented limbs. IVUS was significantly more sensitive ($P = .03$) than venography in estimating residual thrombus burden. However, there was no significant difference in PTS incidence whether the clot was completely lysed or not.**

Conclusions: **Venographic patency can be established in most limbs with DVT or stent thrombosis by PMT alone. Venographic patency was a poor guide to the presence and extent of residual thrombus. Follow-up CDT was useful in significantly increasing complete clot clearance, but residual thrombus remained on IVUS in over two-thirds of treated limbs overall. The implications of residual thrombus after inline flow has been re-established with thrombolytic regimens for the development of PTS are unknown. (J Vasc Surg: Venous and Lym Dis 2014;2:148-54.)**

Pharmacomechanical thrombectomy (PMT) and catheter-directed thrombolysis (CDT) of deep venous thrombosis (DVT) are widely practiced even though utility in terms of prevention of post-thrombotic syndrome (PTS) remains to be definitively proven. Less controversial is the use of these lytic regimens in thrombosis of a previously placed iliac vein stent. In either case, intravascular ultrasound (IVUS) is a useful adjunct, as correctible stenotic lesions that predisposed to the thrombosis are often found after lysis.[1-4] We have noticed that IVUS examination of lysed veins often shows that substantial residual thrombus remains after flow has been reestablished as evidenced by venography. In many instances, the amount and extent of residual thrombus would be alarming with threat of progression if viewed in a fresh untreated limb. This has outcome implications because residual thrombus has been related to the incidence of PTS.[5,6] Most centers currently rely only on venography to assess success of lysis with emphasis on restoration of inline flow.

The purpose of this report is to assess the lytic outcome of thrombolytic regimens in limbs with DVT and/or iliac vein stent thrombosis using both IVUS and venography as assessment tools and to analyze the incidence of residual thrombus and its relationship to PTS in limbs where inline flow had been re-established after lysis, as shown by venography.

Table I. Case materials

Criteria	*DVT (n = 35)*	*Stent thrombosis (n = 32)*
Median age, years (range)	60 (24-79)	57 (25-83)
Male:female	1:1	1:2
Right:left	1:1	1:4
Primary:post-thrombotic	1:2	1:7

DVT, Deep venous thrombosis.

METHODS

A total of 67 limbs in 65 patients underwent thrombolysis by PMT with follow-up CDT over a 7-year period. Thirty-five limbs had DVT (DVT group) and 32 limbs had thrombosis of a pre-existing stent (stent thrombosis group). Lysis was instituted if the thrombus was fresh

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Author conflict of interest: Dr Raju has stock in Veniti.

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Table II. Initial thrombus load in treated limbs

No. of segments[a]	*DVT (n = 35)*	*Stent thrombosis (n = 32)*
1	5	6
2	24	23
3	4	2
4	2	1

DVT, Deep venous thrombosis.
[a]Score of 1 each for inferior vena cava, iliac veins, femoral veins, and popliteal vein. Maximum possible score = 4.

Table III. Restoration of flow (venogram)

	DVT	*Stent thrombosis*	*DVT and stent thrombosis*
PMT	74% (26/35)	91% (29/32)	82% (55/67)
Follow-up CDT (failed PMT)	20% (7/35)	6% (2/32)	13% (9/67)[a]
Total	94% (33/35)	97% (31/32)	96% (64/67)

CDT, Catheter-directed thrombolysis; *DVT,* deep venous thrombosis; *PMT,* pharmacomechanical thrombectomy.
[a]PMT vs PMT/CDT combination <0.03.

by history (<2 weeks) and duplex appearance. The lytic method used and demographic detail of the two groups are shown in Table I. PMT was initially used, and if residual thrombus was still present on IVUS examination, CDT was used for 24 to 72 hours, unless contraindicated by age >60 or potential for gastrointestinal bleeding from prior history. Temporary or permanent inferior vena cava filters were not used in any of the limbs.

Technique of PMT. Trellis (Covidien, Mansfield, Mass) was used exclusively; 10 mg of Activase (Genentech, San Francisco, Calif) was infused into the thrombus per treatment length between exclusionary balloons in 1-mg/min aliquots with activation of the device. Two treatments were required by sequential movement of the catheter to cover long-segment occlusions. After the infusion was complete, device action was continued for another 5 minutes before aspiration of the lysed portion of the clot with deflation of the balloons in sequence as recommended.

Technique of CDT. A thrombolysis catheter of appropriate infusion length was inserted into the thrombus. Activase was infused at 1 mg/h along with heparin 400 units/h. Lytic progress was followed by daily venograms. CDT was continued until lysis was complete or up to a maximum of 3 days. If the flow has been established as shown by venography, the patient underwent IVUS examination to clear residual thrombus by balloon maceration/compaction or for stent correction of detected stenosis. Therapeutic anticoagulation was instituted/continued in all patients in this study after lysis.

Assessment of lytic efficacy. Re-establishment of flow across the thrombosed segment (inline flow) was determined by venography. Completeness of lysis and extent of residual thrombus was determined by IVUS examination. Residual thrombus on IVUS was retrospectively scored 0-2 from operative IVUS description (0 = none; 1 = occupying 50% lumen area; 2 ≥50% lumen area)

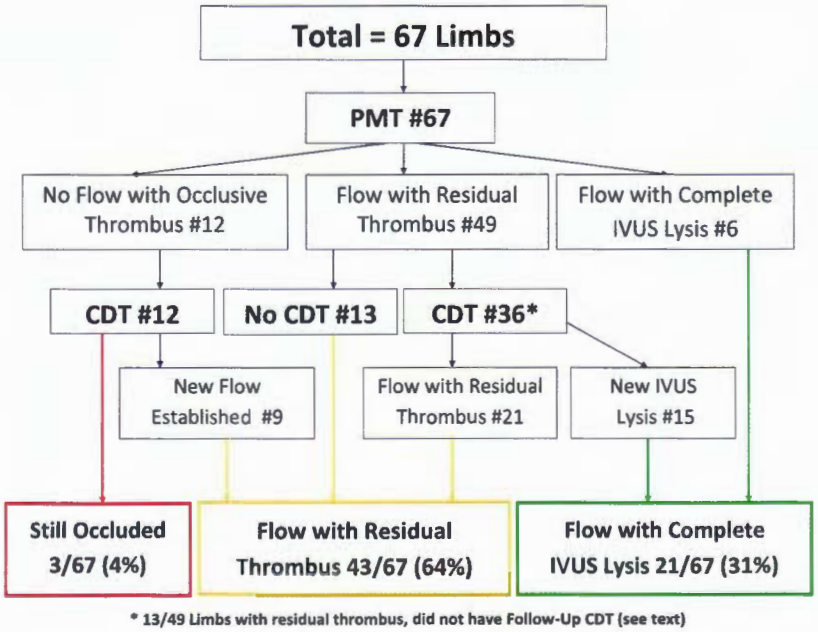

Fig 1. Flow chart showing proportion of limbs with successful thrombolysis (intravascular ultrasound [*IVUS*]). Thrombus was completely cleared in only 9% of limbs after pharmacomechanical thrombectomy (*PMT*) alone and an additional 22% for a total of 31% after both modes of treatment. *CDT,* Catheter-directed thrombolysis.

Table IV. Residual thrombus scores[a] by intravascular ultrasound (*IVUS*) and venography after lysis[b]

	Venography (n = 56)	*IVUS (n = 62)*[c]
Median (range)	1 (0-2)	2 (0-2)
Score of 0	7	5
Score of 1	23	22
Score of 2	26	35

[a]Scoring method of residual thrombus: none = 0; filling ≤ 50% lumen = I; filling >50% lumen = 2.
[b]All limbs had a prelysis score of 2.
[c]*P* value = .03.

slightly modified from venographic scoring method as described by Mewissen.[4]

Clinical assessment of PTS. Patients were examined at 6 weeks and at 3- to 6-month intervals thereafter with clinical and duplex assessment. A venous severity score[7] along with pain assessment with a visual analogue scale (VAS)[8] was recorded at each visit into a time-stamped electronic medical record. Pain was graded from 0-3 for this analysis based on the recorded pain scale: grade 0 = none; grade 1 = VAS 1-3; grade 2 = VAS 4-6; grade 3 = VAS 7-10. Swelling was graded 0-3 per recorded VCSS. Skin changes were as noted in Venous Clinical Severity Score (VCSS).

PTS grading. A PTS grade (0-3) was assigned based on the higher of either pain or swelling grade as described above. Any skin manifestation (VCSS) was automatically assigned PTS grade 3. The above PTS grading is based on the three cardinal features of PTS (pain, swelling, and skin changes). Raw VCSS score by itself was not used in analysis because its pain scale has less resolution, and stocking use (whether prophylactic or therapeutic) inflates the overall VCSS score.

Statistics. Individual data are given as median with range, unless otherwise indicated. Values were analyzed by a two-sided Fisher exact test or two-tailed paired *t*-test as appropriate. Cumulative survival curves were plotted in standard fashion (truncated when standard error of the mean >10%) and significance tested by the log-rank method. Statistical significance was defined as a *P* value of less than .05. All analysis was performed using Prism Software (GraphPad Software, Inc, Irvine, Calif); n values might vary slightly from total treated limbs for certain analysis due to missing data.

RESULTS

Initial thrombus load based on involved segments in treated limbs (modified from Mewissen) is shown in Table II. There was no mortality, clinically apparent pulmonary embolism, or stroke. Two out of 67 limbs (3%) required blood transfusions for access site bleeding/hematoma during lytic therapy. Fifteen out of 35 (43%) limbs in the DVT group received an iliac vein stent to correct an underlying stenotic lesion. Rethrombosis occurred (≤60 days) after lysis in 10 limbs (15%), two of which (one each in the DVT and stent groups) were reopened after repeat lysis. The latter are included in the successful lysis category.

Restoration of flow (venography) and completeness of lysis (IVUS) in the study material is shown in Table III. PMT was successful in restoring flow in the vast majority of thrombosed segments; a total of 55/67 (82%) of treated limbs had restoration flow. Follow-up CDT restored flow in an additional nine limbs that had failed PMT for a total of 64/67 (96%) limbs for the PMT/CDT combination ($P < .03$ vs PMT alone). Thirteen limbs in which PMT failed to lyse the thrombus completely despite inline flow did not undergo follow-up CDT because of age over 60 (10/13), prior history of bleeding, or patient choice.

Complete IVUS clot lysis was achieved after PMT in only six out of 67 (9%) limbs (Fig 1). Follow-up CDT resulted in complete clot lysis in an additional 15 limbs that had failed PMT for a total of 21/67 (31%) limbs for the PMT/CDT combination. Though complete lysis was not achieved, clot burden was reduced to a variable extent (thrombus score of 0 or 1) by the lytic regimens as shown

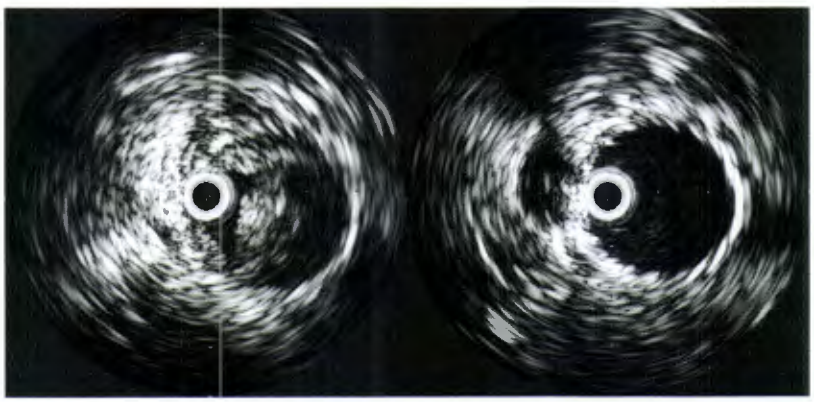

Fig 2. Successful clearance of stent thrombosis by balloon maceration/compaction.

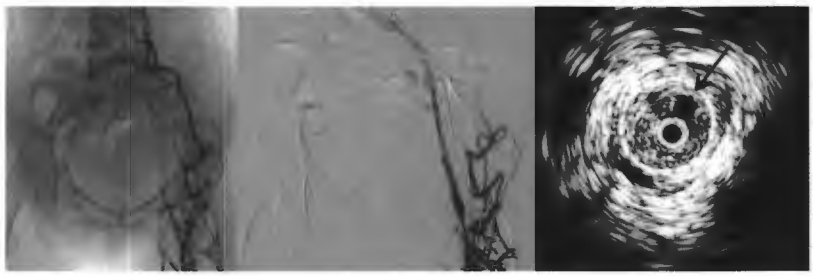

Fig 3. Stent thrombosis **(left)**. Venogram shows restoration of axial flow **(middle)**, but substantial residual thrombus remained **(right)**. Intravascular ultrasound (IVUS) examination shows a small venographic channel (*arrow*) surrounded by thrombus.

in Table IV. All limbs had a thrombus score of 2 (total occlusion) prior to lysis.

Complete clot lysis with PMT-CDT combination was achieved significantly more often in limbs with DVT than in thrombosed stents (43% vs 19%; $P < .04$). Further clot clearance can be achieved in some stented limbs by balloon maceration/compaction (Fig 2), a technique probably not appropriate in virgin veins with residual thrombus. Maceration/compaction was used in five limbs and was successful in three (two after PMT, one after CDT); these limbs are included as successful lysis in the respective subset.

In the limbs with restoration of flow, residual thrombus remained on IVUS examination in over two-thirds of limbs (46/67; 69%). The flow often occurred in these instances through a small channel through the clot and/or around it, and the venographic appearance of restored patency was somewhat deceptive (Fig 3). While residual thrombus could be suspected on venography in many limbs (Fig 4), others had a normal appearance (Fig 5). In most instances, the extent of residual thrombus seen on venography was much worse on IVUS examination (Fig 6). Median residual thrombus score was significantly higher ($P = .03$) with IVUS compared with venography as shown in Table IV; the IVUS score was lower than venography in only two (4%) limbs. The sensitivity of venographic inline flow as a marker for complete thrombus lysis (IVUS) was only 20%.

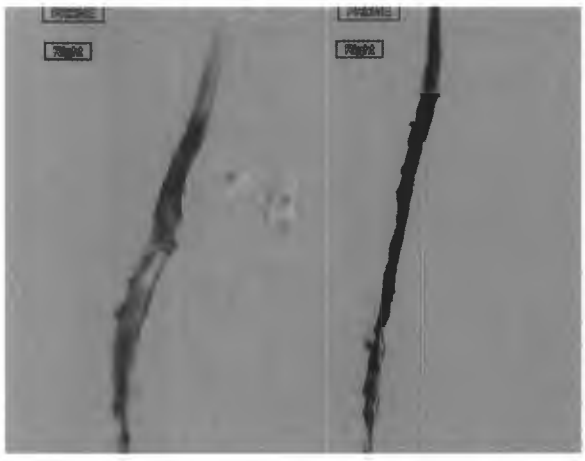

Fig 4. Iliofemoral deep venous thrombosis (DVT) **(left)**. Though venographic flow was restored by lysis, irregular lumen contour suggests residual thrombus.

Incidence of PTS in treated limbs

PTS incidence. Limbs in the stent group were excluded for this analysis because limbs were originally stented for PTS or PTS-like symptoms. Cumulative freedom from onset of PTS by grade severity for treated limbs in the DVT group is shown in Fig 7. At 36 months, only 52% of limbs were free of any PTS manifestations (grade 1 or higher); the incidence of severe (grade 3) PTS features was 30% (70% free). There was no difference in PTS incidence or severity (grade 3) between limbs with complete lysis compared with those with inline flow and residual thrombus ($P > .5$; NS) even after limbs that remained occluded after lysis or rethrombosed were excluded.

DISCUSSION

PMT alone was effective in establishing flow in the vast majority of limbs (82%). Follow-up CDT restored flow in only a small number of additional limbs (13%), increasing flow restoration to 96% overall. However, complete clot lysis was obtained in only 9% by PMT alone, and follow-up CDT resulted in complete clot lysis in an additional 22% for overall complete lysis in 31% of treated limbs (Fig 1); 69% of treated limbs remained with residual thrombus.

Thrombolytic agents bound to the thrombus are known to continue lysis for several hours after infusion.[9,10] Restoration of axial flow itself may help continued autolysis of residual thrombus by circulating plasminogen, reducing eventual thrombus burden. The above intraprocedural IVUS data may, therefore , somewhat overstate the extent and incidence of residual thrombus that persists. Since PMT alone restores flow in the majority of limbs and the lytic agent is delivered between occlusive balloons, it may be considered in patients who are not candidates for CDT because of age or risk of bleeding. This was used in 10 patients safely in this series. Many authors have

Fig 5. Successful venographic lysis of iliofemoral deep venous thrombosis (DVT) **(left)**. Residual thrombus was not suspected based on "clean" venographic appearance **(middle)**. However, intravascular ultrasound (IVUS) examination shows substantial unlysed thrombus **(right)**.

suggested that PMT may be used as the sole form of thrombolysis based on excellent thrombus resolution in parity with catheter lysis.[11-13] The persistence of significant residual thrombus (>50% remaining) following PMT and/or catheter lysis is in the range of 10% to 25% as reported by others[4,11-13] based on venographic assessment. Our own interpretation of postlysis venograms shows a much higher incidence of residual thrombus as shown in Table IV. Differences in technique, lytic agents, and devices used may account in part for this discrepancy. Beyond author bias in interpretations, venographic technique itself lends to misinterpretations. The vein wall (except when stented) and the thrombus itself are radiolucent, and residual thrombus is inferred indirectly from the filling defects in the contrast channel. A smooth thrombus lining the wall will be missed. IVUS is more objective in this regard,[2,3] as identification of thrombus is more direct and factors such as projection angle, flooding or paucity of contrast, and other sources of potential error in venographic interpretations (eg, mistaking a focal thrombus for tributary inflow) are absent. IVUS, though superior in delineating lumen surface morphology, is not well suited to identify flow detail. Venography is clearly superior to assess flow restoration, and IVUS should be viewed as complementary to assess residual thrombus. Others have used IVUS in this fashion[14] with much less residual thrombus incidence than reported herein. This report is not primarily designed to compare relative diagnostic sensitivity of the two methods but to highlight that residual thrombus was present in a high proportion of treated limbs in this series. There are other imaging methods[15-17] that may be more sensitive than venography to detect residual thrombus but are not well suited to influence intraprocedural decisions.

The implications of the above findings for the development of PTS are not clear. We do not know whether restoration of inline flow by itself is enough or whether complete clearance of thrombus is necessary to prevent or lessen the incidence of post-thrombotic syndrome. Recurrent thrombosis, as well as incidence of PTS, appears to be related to residual clot burden.[5,6,18] PTS is now known to be related to combined obstruction/reflux,[19] but the relative importance of these pathologies is not known. It is known that the iliac vein segment is less endowed with collateral potential than the femoral segment.[20,21] Obstruction of the iliac veins is, therefore, likely more important than femoropopliteal-tibial segments[5,20-24] but the issue is far from settled.[25,26] Reflux as a potentiating factor for PTS is a consideration in infrainguinal segments only. Reflux develops in previously thrombosed[27] and uninvolved segments[28] as well. The relative hemodynamic importance of proximal or distal valve reflux also remains unsettled.[29-33] Taken together, these observations mean that the location as well as the extent of residual thrombus will likely influence evolution of PTS by different mechanisms. While residual thrombus is a major factor, numerous other mechanisms are involved in the evolution of PTS.[34] We can expect that reduction of thrombus burden, even if complete by lytic regimens, may diminish the incidence of PTS but will not likely

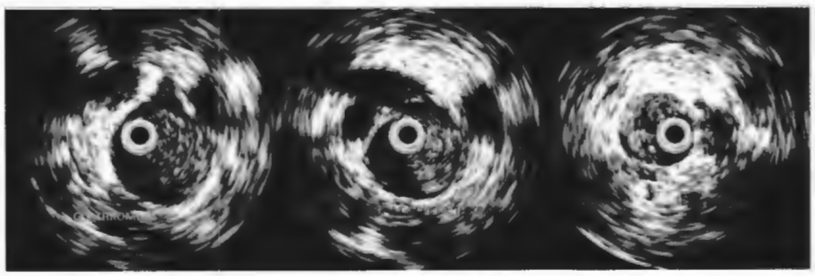

Fig 6. Extensive thrombus in the common femoral vein **(left)**, profunda orifice **(middle)**, and the femoral vein **(right)** as seen on intravascular ultrasound (IVUS) examination in the same limb shown in Fig 4.

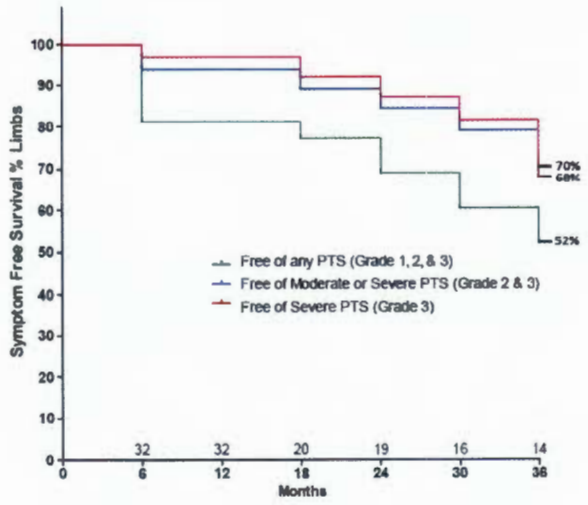

Fig 7. Cumulative freedom from post-thrombotic syndrome (*PTS*) after thrombolysis. Limbs with residual thrombus and without are both included. The incidence of any PTS at 36 months was 48% (52% free); 30% had PTS (70% free at 36 months).

eliminate it, as evident in Figs 6 and 7. Within the limits of this somewhat unknown boundary, complete over partial thrombus lysis may possibly make a difference at the margins in PTS outcome. The data presented here fail to provide supporting evidence for this. Nevertheless, the issue remains open because of the many weaknesses of the study, particularly in assessing PTS outcome. The current analysis suffers from small sample size, retrospective design, and PTS scoring as well as absence of nonlysed DVT controls.

Given the current uncertainty, we suggest the use of CDT after PMT in patients who can tolerate it safely to achieve complete thrombus clearance. This is partly based on practical considerations, as the window of opportunity for complete clot lysis is time-limited and will be irretrievably lost if complete lysis is shown to be important sometime afterward. Informed consent with full discussion of the risks and uncertainties of this approach is essential.

AUTHOR CONTRIBUTIONS

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

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