Dethrombosis of the Lower Extremities: Pharmacologic and Mechanical Techniques

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Abstract

Thrombus is widely present in the peripheral vasculature and its frequency depends on the patient’s clinical presentation. Thrombus is almost always present in acute critical limb ischemia (ALI) and is commonly found in patients with subacute presentations, chronic critical limb ischemia (CLI) and chronic occlusions. The approach to dethrombosing a vessel depends on multiple factors, including the age of the thrombus, but generally requires a combination therapy with chemical lysis and rheolytic thrombectomy, such as the use of Power-Pulse Spray (PPS) technique, or atherectomy with dethrombosing capability such as the excimer laser. Surgery, or chemical lysis as a standalone therapy, carries very high rates of amputation and mortality.

The role of embolic protection devices is still unclear but is promising, as embolization of atherothrombus continues to be a frequent occurrence during peripheral angioplasty. In this review, algorithms to treat thrombus in peripheral arterial disease are suggested.

Introduction

Peripheral vascular disease (PVD) is thrombogenic. There is a high frequency of elderly patients, diabetics, hyperlipidemics and smokers, conditions associated with hypercoagulation, who present with PVD. In addition, patients with PVD have a heightened inflammatory state, leading to plaque rupture and subsequent acute and subacute thrombosis and embolization, a mechanism similarly seen in unstable coronary syndromes. Furthermore, patients with PVD have a higher incidence of coexistent coronary disease, myocardial infarction (MI), congestive heart failure and arrhythmias, conditions associated with thromboembolism. Finally, occlusions in the peripheral vasculature are likely to contain atherothrombus, usually multilayered acute and/or subacute.

The angiographic presence of thrombus depends on the acuity of the presentation. For instance, fresh thrombus is the hallmark of acute limb ischemia (ALI), present in 100% of these patients. In a recent study, thrombus was present in 16.7% of a PVD population, with 34.4% of these patients having had a recent onset of symptoms. In contrast, only 3% of patients had angiographic thrombus in an elective population undergoing renal, iliac and femoral percutaneous interventions, with long occlusions excluded. Despite these differences, angiography considerably underestimates the true presence of thrombus, particularly in patients with chronic occlusions.

The presence of thrombus in the peripheral vasculature is associated with multiple complications, including amputation, death, higher re-occlusion rates, urgent/emergent surgical revascularization, embolization, longer procedure times (Figure 1), prolonged hospitalization, and the need for the use of a high level of anticoagulation, generally associated with increase in major bleeding. Effective and safe treatment of thrombus is therefore of critical importance to reduce complications during peripheral percutaneous interventions (PPI).

The approach to treating thrombotic lower arterial disease depends considerably on the acuity of the presentation. Generally patients are divided into three categories: 1. Acute Presentation. This generally occurs within hours of presentation and is associated with rest limb pain and a pulseless, painful foot. The vessel is typically occluded with a thrombus that has occurred on top of mild to severe lesions. Collaterals are generally minimal or none. The mechanism of acute thrombosis is mostly plaque rupture followed by in-situ thrombosis or migration of a clot distally. In addition, and not infrequently, embolization of a proximal thrombus in patients with MI, arrhythmias and congestive heart failure is seen. Thrombi in these patients tend to be fresh, and an emergent intervention is needed to salvage the limb. This presentation is referred to as acute critical limb ischemia (ALI). 2. Subacute Presentation. This generally occurs within days to a month. The patient typically presents with accelerated limb pain, with minimal activity or at rest. The underlying lesions are usually severe. A high frequency of total occlusions is seen. Typically patients have collaterals, but not enough to sustain adequate lower extremity circulation at rest or with minimal activity. In subacute presentations, there is a high likelihood that a recent thrombus is present, probably...
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Figure 1. Procedure time in patients undergoing percutaneous peripheral intervention of the lower extremity, with or without the presence of a thrombus.

organized, and likely overlying additional subacute and chronic thrombus. The presentation of these patients is analogous to unstable coronary syndromes. Patients typically have limb pain with minimal activity [Rutherford-Baker classification (R-B) III], or at rest such as in critical chronic limb ischemia (CLI).

3. Chronic Presentation. This generally occurs within several months to years. The presentation is typically moderate to severe claudication (R-B II and III). In this population, underlying chronic occlusions can occur in about a third of patients. Collaterals are well-developed but remain suboptimal to keep the patient symptom-free. The presence of angiographic thrombus in this patient population is low, but it is our experience that organized thrombus is likely to be present in the majority of chronic occlusions. These patients are analogous to stable angina patients.

As noted, the clinical presentation of the patient is a substantial factor that influences lower extremity thrombus treatment and will affect the technique and anticoagulant of choice periprocedurally. The anticoagulant should be able to prevent further platelet and thrombin activation, reduce macro/micro thrombus downstream, be very effective in penetrating and dissolving existing thrombus, have lower reocclusion rates and be associated with low bleeding complications. Techniques utilized need to effectively restore flow, minimize procedure length, dissolve thrombus in association with the anticoagulant, reduce embolization downstream and have favorable long-term results.

Taking all of the above factors in consideration, we suggest the following algorithms for the treatment of patients with thrombotic lesions. We understand that more research is needed to validate these recommendations, which are based on the best currently available data.

Base Anticoagulant in PPI

PPI is thrombogenic. Thrombin activation is universal with vascular injury and recent data suggest that it is not easily suppressed by high-dose unfractionated heparin (UFH) alone or low-dose heparin combined with intravenous antiplatelet drugs. UFH leads to unpredictable activated clotting times.

Suggested Treatment Algorithm for ALI

Thrombolysis or surgery alone carries a very high risk of amputation and death, and therefore new therapeutic approaches have been evaluated. Figure 2 shows the suggested algorithm for the treatment of ALI. We believe that in the setting of ALI, thrombus is generally fresh, and
the first attempt to remove it is by rheolytic thrombectomy (RT) with the AngioJet system (Possis Medical, Inc., Minneapolis, Minnesota) that operates by creating a local vacuum through internal high-speed jets, resulting in aspiration and dissolution of the thrombus. In a retrospective multicenter data review of 99 consecutive patients (male = 52) with ALI, the mean age of 67 years received AngioJet thrombectomy as a first-line treatment (native arteries, n = 88; bypass grafts, n = 19). Complete resolution of thrombus was seen in 70.7% of patients, partial resolution in 22.2%, and no change in 7.1%. Adjunctive thrombolysis post AngioJet thrombectomy was used in 37 patients (37.4%). Non-emergent surgical revision was performed in 3 patients (5.1%). In-hospital complications included death in 4% of patients, 2 major amputations, 5 cases of minor tissue loss, and 7 rethrombosis. Mortality and amputation rates at 30 days were 7.1% and 4%, respectively.

Although the AngioJet system alone was very effective, a third of patients required the addition of thrombolysis. Alie et al. recently reported their technique of the Power Pulse Spray in patients with ALI. In this technique, the outflow port of the AngioJet catheter was closed, and then the catheter was advanced at 1-mm increments while pulsing lytic agent within the thrombus. In their study, 49 patients with i iliofemoral thrombotic occlusions were included. Group I (n = 25) received 10–20 mg of tenecteplase (TNK)/50cc saline. Group II (n = 24) received 1,000,000 Units Urokinase (UK)/50cc saline. The procedure success was 92% and 91.6%, respectively. Procedure time was considerably short in both groups at 72 and 75 minutes, respectively. In both groups, 30-day limb salvage was 91%.

Our approach to ALI treatment is AngioJet embolectomy, first using bivalirudin as a base anticoagulant combined with a GPIIb/IIIa inhibitor. Recent data in the periphery in CLI patients suggested that the combination of bivalirudin and GPIIb/IIIa inhibitors does not lead to an increase in bleeding rates, and appears to be more effective than UFH alone in reducing reintervention and limb salvage rates at 6 months. Although randomized data is lacking to compare UFH to bivalirudin alone, or with GPIIb/IIIa inhibitors in the periphery, patients with ALI generally present within hours of symptom onset, and mostly have not been on aspirin or ADP-receptor antagonists such as clopidogrel. Adding an intravenous platelet antagonist for immediate platelet inhibition in this setting appears to be a logical step to reduce further platelet activation, aggregation and embolization. If treatment with the AngioJet system, bivalirudin and GPIIb/IIIa inhibitors does not result in effective thrombus removal, then the Power-Pulse spray (P-PS) technique is utilized. The infusion of a thrombolytic, along with a GPIIb/IIIa inhibitor, has been shown in a randomized trial (Platelet Receptor Antibodies in Order to Manage Peripheral Arterial Thrombosis — PROMPT) to reduce the combined endpoint of surgical revascularization or limb amputation. We believe that the combination of bivalirudin, a GPIIb/IIIa inhibitor and a thrombolytic agent, the latter infused under high pressure directly into a thrombus, is highly effective in treating ALI. In the event that the above measures do not lead to effective restoration of normal flow and thrombus removal, continuous thrombolysis infusion (TNK 0.25 to 0.5 mg/hour for 7–8 hours) via an infusion catheter, along with intravenous GPIIb/IIIa inhibitors, is then initiated, assuming some flow has been previously restored with the P-PS. If no flow has been established with the P-PS, then urgent surgical intervention needs to be considered in an attempt to save the limb.

**Suggested Treatment Algorithm of Subacute/Chronic CLI**

Figure 3a and b show potential algorithms in the treatment of subacute and CLI. In both algorithms, the patient

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**Figure 2.** Suggested algorithm for the treatment of patients with acute critical limb ischemia (ALI).
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**Figure 3a.** Suggested algorithm for the treatment of patients with chronic critical limb ischemia (CLI).

**Figure 3b.** Suggested alternative algorithm for the treatment of patients with chronic critical limb ischemia (CLI).

is pretreated with aspirin and clopidogrel at least 24 hours prior to the procedure. Bivalirudin is then utilized as a base anticoagulant. In the first algorithm (Figure 2a), the P-PS spray technique is utilized first, as we believe the AngioJet alone tends to be less effective in organized thrombus removal. GPIIb/IIIa inhibitors are not infused at this point since the patient has already been pretreated by oral antiplatelet drugs. Following the P-PS, a wait period of 20 minutes is then allowed and AngioJet embolectomy performed. Treatment of the underlying lesion is then carried out. GPIIb/IIIa inhibitors are only used as a bail-out if more thrombus or continued slow flow is seen.

The alternative algorithm (Figure 3b) is mostly based on the combined use of a GPIIb/IIIa inhibitor with bivalirudin as an initial anticoagulant strategy. The Cardiovascular Institute of the South investigators recently reported the feasibility of this approach. In their study, 149 CLI patients received tirofiban and bivalirudin and were compared to a historic 149 CLI patients who received UFH alone. The rate of reintervention (10.7% versus 18.8%, p = 0.0301) and limb salvage (93.5% versus 88.5%, p = 0.053) at 6 months was in favor of the combined bivalirudin and GPIIb/IIIa inhibitors. Also, a trend toward more embolization was reported with the UFH group compared to the bivalirudin-GPIIb/IIIa inhibitor group (5.4% versus 1.6%). Further prospective studies are needed to validate either approach.

Treatment of the lesion can be carried on with various techniques, ranging from balloon angioplasty to laser, or Silverhawk atherectomy (Fox-Hollow Technologies, Inc., Redwood City, California) and/or stenting as needed.

Recent reports showed favorable results with ablative atherectomy techniques in CLI. The superiority of a particular technique over others, however, has not yet been established in randomized clinical trials.

In the limb salvage following Laser-Assisted angioplasty for Critical limb Ischemia (LACI) trial, 145 patients (155 critical limbs) judged to be poor candidates for bypass surgery were prospectively enrolled in 14 sites to
receive treatment with laser and balloon angioplasty. In this registry, occlusions were present in 92% of limbs and stenting was implanted in 45% of vessels. Procedural success was seen in 85% of limbs and at 6-month follow-up, limb salvage was achieved in 92% of patients. The advantage of laser angioplasty is the ability of the cold excimer laser (Spectranetics Corporation, Colorado Springs, Colorado) to ablate both plaque and thrombus, therefore playing an important role in the dethrombosis process. Silverhawk atherectomy also seems to be effective in treating patients with CLI. Kandzari et al.20 recently reported data on 69 patients (76 limbs) treated with the Silverhawk atherectomy device in 7 institutions. No unplanned limb amputations were reported in 6 months. Embolization was not observed in this study, although data from a separate study21 using embolic protection devices showed that in 10 patients undergoing atherectomy, debris was collected distally in all patients. The consequences of large debris migrating distally are quite obvious, but the clinical significance of small debris is unknown. Although embolic protection devices are not approved or commonly used in the periphery, we believe that they might play a significant role in the future, as the rate of continued atherothrombotic embolization remains significant with percutaneous balloon intervention or atherectomy.

In conclusion, thrombus is abundant in the periphery, particularly in CLI, subacute presentations, CLI and chronic occlusions. Chemical lysis or surgery alone carries a high rate of amputation and mortality. The choice of the anticoagulant and the technique depends on the acuity of the presentation. Generally, a combined chemical lysis and rheolytic thrombectomy appears to be an effective strategy. Bivalirudin is currently the base anticoagulant we use in these patients. GPIIb/IIIa inhibitors and thrombolysis are added as described above. Laser atherectomy is emerging as an important tool in dethrombosing vessels. Embolic protection devices are promising, but more data is needed before they become routinely used in PPI.

References