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Seminars in Vascular Surgery**Fighting Foot Ulcers and Preventing Amputation in the Diabetic Population****Guest Editor: Carlo Setacci****ACUTE ON CHRONIC LIMB ISCHEMIA: FROM SURGICAL EMBOLECTOMY & THROMBOLYSIS TO ENDOVASCULAR OPTIONS****Authors:**

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ABSTRACT

After the invention of the balloon catheter by Fogarty in 1963, surgical thromboembolectomy was considered the gold standard treatment for many years in patients with acute lower limb ischemia (ALLI). ALLI is a dramatic event, carrying a high risk of amputation and perioperative morbidity/ mortality. The evolution of endovascular technologies has resulted in a variety of therapeutic options to establish arterial patency. In the 1970s Dotter first introduced the idea of clot lysis in the treatment of ALLI that was modified to catheter-directed thrombolysis, and now clot aspiration techniques. The majority of ALLI events are due to arterial thrombosis in a patient with preexisting peripheral arterial disease (PAD). The clinical condition of atherosclerotic plaque thrombosis, referred to as “acute on chronic ischemia”, is more to treat than embolic ALLI. Although surgery is still a treatment option especially for ALLI, endovascular interventions have assumed a prominent role in restoring limb perfusion. In this review, the treatment options for ALLI are detailed - from surgical thromboembolectomy to thrombolysis, and current endovascular techniques including mechanical fragmentation, rheolytic thrombectomy and aspiration thrombectomy. The evolution to endovascular therapies has resulted in improved clinical outcomes and lower rates of morbidity.

Keywords: acute ischemia, endovascular intervention, peripheral arterial disease

INTRODUCTION

Epidemiology

Acute lower limb ischemia (ALLI) is defined as any sudden decrease in limb perfusion causing a potential threat to limb viability in patients who present within two weeks of the acute event¹. The incidence of this condition is approximately 15 cases per 100.000 persons per year². The prevalence is <0.1% in general population and about 5-10% in patients with other risk factors for cardiovascular disease, like diabetes or previous cardiovascular events.

Acute lower limb ischemia is still considered to be a dramatic event, carrying a risk of amputation between 15 and 30% and a high perioperative morbidity and mortality (20-30%)^{3,4,5,6,7,8}. Concomitant underlying diseases, the metabolic derangement that seems as a result of the acute insult, and a possible reperfusion injury following revascularization may account for this severe prognosis.^{9,10,11}

The natural history of any ALI is characterized by the rapid onset of ischaemia and by the tissue injuries when the ischaemia persists. The sudden cessation of blood supply and nutrients to the metabolically active tissues of the limb, including skin, muscles and nerves, is responsible for tissue damage and cell death. Firstly energy metabolism shifts from aerobic to anaerobic process, then established ischaemia leads to cell dysfunction and death.

The rapidity of evolution of any ALI event is related to general and local factors. Systemic hemodynamic conditions are really crucial, since an acute arterial occlusion could be almost completely compensated if systemic blood pressure is satisfactory. On the other hand extension of thrombosis can occur in case of hypercoagulable concomitant acute episode or real thrombophilic states¹². Local factors influencing natural history of ALI include the site of occlusion (i.e. more proximal location of clot causes a severe ischaemia due to the lower possibility of compensation by the collateral circulation) and a pre-existing chronic ischaemia, which typically promotes formation of collateral circulation that can ensure distal compensation during an acute event. However an acute occlusion of these collaterals can determine rapid secondary thrombosis of the whole arterial tree.

Etiology and clinical presentation

The etiology of ALLI can be roughly distinguished in two large categories: thrombosis and embolism. Distinction of these two conditions is important because treatment and prognosis are different.^{13,14}

The embolic disease is characterized by the presence of a foreign body (embolus) that partially or completely occludes the vessel lumen. The etiology of embolism is changing; before 1950, the majority of ALLI (~60%) was caused by rheumatic heart disease; today that figure is about 8%. Nowadays cardiac emboli are commonly associated with atrial fibrillation or mural thrombus after a myocardial infarction. Rarely, the embolus arises from valve vegetation or from an atrial myxoma. Emboli may also arise from aneurysms, so the abdomen and popliteal fossa should be palpated carefully. Atheromatous arteries may also cause distal emboli in case of plaque rupture.

In some cases embolism may occur on pathologic artery. This condition is typical of diabetic elderly patient with a cardiac source of emboli (i.e. atrial fibrillation) and asymptomatic femoro-popliteal artery disease. The embolism causes the acute blood flow blockage at level of stenotic segment, with consequent thrombosis of collateral vessels causing a severe acute limb ischemia (Fig. 1a). This kind of embolism should be considered and treated as arterial thrombosis.

Currently, the majority of ALLI (about 70%) is arterial thrombosis, which generally occurs in the setting of preexisting vascular lesion. This condition is quite common in patients with diabetes. Clinical presentation in case of thrombosis on atherosclerotic stenosis (so called "acute on chronic ischemia") may be less severe than in patients with embolic occlusion, as with the former there may be sufficient collaterals present (fig. 1b), but treatment is generally more challenging than ALLI due to embolism.

It's essential to obtain information about any history of claudication or rest pain, and to look for the changes associated with chronic ischaemia such as atrophy of skin appendages, and to examine the

opposite leg for loss of pulses and the presence of bruits. Unfortunately diabetic patients may present with severe atherosclerotic lesions and pauci- or asymptomatic appearance, because of neuropathy and/or a poorly active life. Extreme low-flow states can produce ALLI in patients with hypovolemic shock or cardiac failure, especially when chronic peripheral arterial disease (PAD) is already evident.

Prompt recognition of signs and symptoms is clearly the key point for the management of ALLI. The morbidity and mortality of this acute event is deeply related to the overall medical condition of the patients, to the severity of ischemia at presentation and to the promptness of diagnosis and management.

Physical examination should be focus on the presence of one or more of the “six P” (pain, pallor, paralysis, paresthesia, pulselessness, poikilothermia). At same time the history of the status of lower limb before the acute event should be collected, since it can reveal important clinical clues about the etiology of the current event. Patients with a clear source of emboli and with no history of intermittent claudication or previous vascular intervention, and with normal contralateral limb are probably suffering from embolization; patients with history of PAD, diabetes, claudication or previous vascular intervention, with contralateral limb suggestive of PAD, and with no identifiable source of emboli are probably suffering from thrombosis.

SURGICAL INTERVENTION

Surgical arterial thromboembolectomy

Surgical arterial thromboembolectomy (TE) using a balloon catheter was originally introduced by Thomas Fogarty in 1963¹⁵, and it has been the corner-stone of ALLI's therapy for decades. This specific technique has several advantages, especially in limb-threatening ischemia due to embolic occlusion: it can be quickly performed using local anesthesia, via femoral approach, and it is considered to be not a very complex intervention. It is also the typical case for training for less experienced or young operators. Balloon catheters are passed through the thrombus several times until blood clot is removed and limb perfusion is restored.

When the thrombosis includes below-the-knee (BTK) arteries, surgical approach is more technically demanding. A blind BTK embolectomy has low success rates with an inguinal incision due to the low torquability of catheters.

Thus, TE using Fogarty balloon catheter is a very efficient treatment for acute arterial emboli of lower limbs, especially when a single large vessel is involved¹⁶, but the early clinical outcome still remains unsatisfactory in a number of cases¹⁷, especially when small arteries of the lower limb are involved in the occlusion, or in presence of PAD. It has been well established that intra-operative angiography after TE may frequently detect arterial imperfections, such as incomplete restoration of perfusion in BTK arteries, propagation of thrombi or presence of underlying steno-occlusive lesions^{18,19}, which may be responsible for the early failure. Notably, even vessel injuries secondary to balloon catheter passage may limit the clinical success rate.

Diabetic subjects, who carry a higher risk of developing a severe PAD usually located in BTK vessels, are at high risk of unsatisfactory outcomes after TE using Fogarty balloon catheter. In diabetic patients arteries' walls are typically fragile, tending to spasm, or are very calcified and difficult to reach by Fogarty's catheter cannulation. Moreover, considering the above-mentioned complexity in clinical presentation of ALLI in diabetics (typical signs hidden by the presence of supplementary collateral circuits and diabetic neuropathy) diagnosis may be delayed, making the blood clot more stable and less responsive to treatment.

Different surgical approach, especially when inflow and outflow procedures are requested, are essentials for more demanding pathology's patterns. By-pass procedures may be requested as primary option in these cases or as a second-line treatment when thrombo-embolectomy fails.²⁰

Hybrid treatment

While improvements in surgical techniques and perioperative patient care have occurred over the years, the results available document a persistently high medical need for patients presenting ALLI, with a reported 30-day amputation rate of 5-12%, mortality risk of 10-38%, and combined incidence of amputation and death of 25% to 37.5% at 6-month follow-up^{21,22,23,24}. In clinical practice there is a discrepancy between the immediate technical success of arterial thromboembolectomy that often seems adequate, and the early clinical outcome that still remains unsatisfactory in a number of cases. This incongruence may be related to the incomplete restoration of perfusion due to residual thrombus in distal vessels inaccessible to the balloon embolectomy or to the propagation of residual thrombi. Both historical experimental and clinical studies have shown that clot removal is frequently incomplete after TE, with persistent thrombus demonstrated angiographically and by fiberoptic angiography in small distal vessels in 36% to 82% of patients^{18,19}.

The first attempt to improve the surgical technique for treating acute arterial occlusion was described by Parsons et al. in 1996²⁵. Suggesting the use of intra-operative fluoroscopy and the performance of fluoroscopically assisted thromboembolectomy, the authors described the first example of combination of surgical and endovascular technique for treatment of ALLI. This original hybrid procedure turned out to improve the technical success of TE. Facilitating the catheter passage through tortuous or diseased arteries, this new technique minimized arterial damage and blood loss during clot removal. It had also the potential to facilitate accurate identification, localization, and treatment of significant concomitant arterial lesions.

Since then it has been recommended to perform a routine angiography after TE^{26,27}, but adherence to this recommendation is still limited in clinical practice²⁸.

Completion angiography after TE can not only identify residual thrombus in distal vessels, but also incomplete recanalization of more proximal arteries due to residual thrombus strongly adherent to the arterial wall, or can reveal the presence of significant underlying steno-occlusive lesions after clot removal. In a limited number of cases angiography can even demonstrate the existence of vessel injuries secondary to incorrect balloon catheter passage (fig. 2). These points clearly call for a routine and accurate intra-operative assessment of the adequacy of clot removal, which may be performed by angiography, angiography or IVUS.

It has been a common belief in the past to rely on the presence or absence of back-bleeding from a peripheral arterial bed as a guide to distal arterial patency. Actually, we know that visual evaluation of outflow may be ambiguous to truly prove that adequate circulation has been restored, since irregular thrombotic material may be present in approximately one third of cases²⁹, and back-bleeding may be quite misleading in cases of adequate collateral circulation, despite the occurrence of total distal obstruction.

The central role of intra-operative angiography after TE in defining the need for as well as guiding adjunctive endovascular procedures (so called "hybrid" treatment)^{30,31} has been recently demonstrated. A strategy including hybrid solutions seems to be the keys for better early and mid-term outcomes of ALLI patients.

THROMBOLYSIS

Catheter-directed thrombolysis

Alternative to surgery, percutaneous thrombolysis has been proposed as a procedure less invasive and less demanding for the patient. Being described by Dotter in 1974³², the first results of systemic thrombolysis were not very encouraging: the treatment was unsuccessful in a number of cases and was burdened with a high rate of bleeding complications. Therefore, improvement of thrombolysis resulted in catheter-directed thrombolysis (CDT), which is now widely employed in clinical settings, especially when patients present with less severe ischaemia (classes 1, 2a or sometimes 2b, Rutherford classification of ALLI)

With CDT, the thrombolytic agents are administered through an endovascular catheter near the occlusive blood clot to achieve the complete dissolution and to have the least number of systemic consequences. The preliminary arteriography can precisely detect the location, the length of the occlusion and the presence of collateral circuits. Usually a multi-side catheter is advanced the thrombus and the thrombolytic agents are deployed for a period ranging from 12 to 72 hours based on the severity of ALLI, and to the patient's response to the therapy. Contemporary continuous unfractionated heparin infusion is administered to prevent re-thrombosis and peri-catheter thrombosis.

Different protocols of CDT are usually used: continuous infusion, pulse/spray and a combination of both.⁽¹¹⁾ A Cochrane systematic review showed that the greater benefit is seen when the thrombolytic agents are delivered within the thrombus. "High dose" and "forced infusion" techniques, or adjunctive agents such as platelet glycoprotein IIb/IIIa inhibitors may speed up thrombolysis, but these are not accompanied by lower amputation rates or a decreased need for adjunctive endovascular or surgical procedures. "Low dose continuous infusion", following initial lacing of the thrombus with a high dose of the thrombolytic agent, is the least labor-intensive technique. There is no evidence that a specific regimen is more effective than the others.³³

Nowadays all clinical available agents are forms of plasminogen activators. They act through the conversion of plasminogen to plasmin, which is able to degrade fibrin. The first agent was developed in 1940's and it was called Streptokinase. Through the years other agents were discovered, as Urokinase, more innovative substances as recombinant tissue plasminogen activator (rt-PA). A recent systematic review showed that intra-arterial rt-PA is more effective than intra-arterial streptokinase or intravenous rt-PA in improving vessel patency in people with peripheral arterial occlusion. There was no evidence that rt-PA was more effective than urokinase for patients with peripheral arterial occlusion and some evidence that initial lysis may be more rapid with rt-PA, depending on the regime. Incidences of hemorrhagic complications were not statistically significantly greater with rt-PA than with other regimes. However, all of the findings come from small studies and a general paucity of results means that it is not possible to draw clear conclusions.³⁴

CDT has been used as an alternative to surgical embolectomy for ALLI with gratifying results, but its success is related to the ability to pass a guide through and embed a multisided catheter into the occlusion^{35,36}. Thrombus removal is reported in 75% to 92% of cases.¹³ However it carries a significant risk of bleeding complication during and after drug infusion. In TOPAS trial⁸, 12.5% of treated patients had major hemorrhagic events, including a rate of 1.4% of intracranial hemorrhage. The risk of bleeding was increased up to 19% when heparin was contemporary used.

Results from randomized trials comparing surgical embolectomy to CDT reveal that thrombolysis has the greatest advantage in acute prosthetic bypass graft occlusions, while patients with ALLI due to native arterial occlusions tend to be associated with inferior results after thrombolysis, consisting in higher rates of hemorrhage and stroke at 30 days, and increased risks of distal embolization.^{37,38}

Recently, it has been proposed to combine CDT target lesion endovascular/surgical correction to guarantee an optimal treatment outcome and better long-term patency (see "hybrid treatment" section).^{30,39}

Ultrasound-accelerated thrombolysis

The employment of ultrasound waves has been proposed to facilitate mechanical fragmentation of the thrombus and increase the speed of clot disruption. The ultrasound producing devices (EkoSonic® Endovascular System, Ecos, Bothell, USA and Trellis™ Peripheral Infusion System, Ev3, Plymouth, USA) are placed directly in the thrombus, where micro-transducers transmit high-frequency low-power sound waves. The fibrin is made thinner by the ultrasonic power and breaks consequently. As a result, plasminogen receptor sites are exposed and the thrombolytic agent may penetrate deeper in the thrombus, accelerating the absorption of rt-PA and the thrombus lysis^{40,41}.

Vibrations produced directly by the therapeutic catheter in Trellis™, enhance the clot disruption, reducing the time of the procedure and total amount of utilized PA together with the risk of bleeding.^{42,43} Moreover, the Trellis™ system is provided with a dedicated catheter with two protective balloons at the proximal and distal ends of the working segment, that are specifically designed to reduce the risk of distal embolization. Inflating the two balloons (maximum diameter 14 mm) provides isolation of the vessel: the thrombolytic agent is infused with an oscillated wire and then aspirated. The system is projected to maximize the effect of thrombolysis and minimize the systemic dispersion of thrombolytic agents.⁴⁴ Schrijver A et al. showed a 97% initial technical success with ultrasound emitting devices, followed by a 77% overall clinical success with median thrombolysis time of 21 hours.⁴⁵

ENDOVASCULAR INTERVENTION

Percutaneous mechanical thrombectomy devices have been proposed over the past two decades to speed up the time required for dissolution of thrombus by pharmacologic means, and to reduce the amount of thrombolytic agent used.⁴⁶ The first devices were developed for aspiration and dissolution of small amounts of thrombotic material during coronary procedures, while the clot quantity in cases of ALLI may be much larger, making complete clot removal more challenging. Thus, continuous efforts to develop dedicated devices to ALLI have been made by the industry, and several new treatment tools have been proposed.

Manual aspiration thrombectomy is the first percutaneous approach for clot removal, followed by a series of mechanical thrombectomy based on different mechanism of action (mechanical fragmentation, aspiration, rheolytic thrombectomy and their combinations).

Manual aspiration

The first method of percutaneous arterial thrombus removal was manual aspiration thrombectomy (MAT) via large lumen⁴⁷ Initially, it was described as rescue maneuver in case of distal embolization during endovascular procedure⁴⁸, by using large lumen end-hole aspiration catheters from 5 to 9 Fr, depending on the diameter of the artery occluded.

Afterward, suction is produced using a 20–50 ml syringe while withdrawing the catheter, and thrombus is typically removed after a series of catheter passages. Even though the procedure is really low-cost and may offer some acceptable results, with published technical success up to 96.6 %⁴⁹, MAT may have less satisfactory outcomes in cases of old and well organized thrombus, and in patients with disseminated atherosclerotic, as typically diabetic patients are. In such cases unintentional vessel damage by multiple passages of catheters not specifically designed for this purpose is high. Moreover keeping constant aspiration can be challenging: the manually induced negative pressure can be too high causing collapse of the catheter tip, or it can falls down very quickly triggering a partial lost of the thrombotic material from the catheter and consequent distal embolization. All these potential drawbacks justify why MAT has never gained wide consensus among physicians.

Mechanical fragmentation

The Rotarex (Straub Medical AG, Wangs, Switzerland) is a mechanical thrombectomy system with a working catheter consisting in a fast-spinning head (40,000 – 60,000 rpm) driven by a rotating helix inside it. The fast-spinning mechanism generates a vortex that first separates the thrombus from the artery wall and then fragments it. According to the Archimedes screw principle, clot is subsequently aspirated inside the catheter through the aspiration ports located just behind the head. Direct contact with the vessel wall may cause different type of damage up to artery perforation. The device is available in 6 and 8 Fr diameter versions, which allow effective thrombectomy from iliac to tibial arteries. In a series of 98 patients with acute and subacute thrombotic arterial and bypass graft occlusions, Zeller et al. reported early technical success in 92 % of cases with a reasonable complication rate.⁵⁰ Recently, Heller et al. reported a high technical success is a single center series of 147 acute limb ischemia using Rotarex, especially when in association to limited thrombolysis (90.5%).⁵¹

Technical success may be limited in case of acute on chronic ischemia, even though published data are controversial. Lagana et al. reported that technical success of Rotarex is limited in case of thrombosis complicating calcified plaques or dissection intimal flaps. It may even cause rupture of the arterial wall. In their experience, in cases of subacute and chronic occlusions of by-pass grafts, stents and stent grafts, and other additional procedures are necessary to achieve complete recanalization.⁵² Instead, Kronlage et al. showed that the use of rotational thrombectomy in the treatment of subacute critical limb ischemia is not inferior to local thrombolysis and is associated with a lower complication rate, shorter duration of

hospitalizations, and a lower cost of and lower costs in a 12-month follow-up in a tertiary hospital collective.⁵³

The Jetstream(R) Atherectomy System (Boston Scientific, Marlborough, USA) consists of a single-use catheter provided with four cutting front blades located just behind a rotating tip. The device diameter ranges from 1.6 to 3.4 mm, allowing effective treatment of vessels from the groin to the ankle. Disrupted material is evacuated via suction ports located behind the rotating tip. To minimize the risk of peripheral embolization, the vessel is constantly flushed with saline through infusion ports located proximally to the aspiration ports.

The system is engineered to predictably treat multiple morphologies, such as calcium, plaque or thrombus, commonly found in total occlusions, and ideally can be of great benefit in case of acute on chronic vessel occlusion in diabetic patients. Evidence of its efficacy is well described in literature in case of chronic vessel occlusion or in-stent restenosis^{54,55}, while it remains still under-investigated in case of acute limb ischemia.⁵⁶ Still, abrupt vessel occlusion, dissection, distal emboli, hematoma at access site, infection, perforation, pseudoaneurysm, renal failure, restenosis, and thrombus formation are some of the reported complications of Jetstream atherectomy.⁵⁷

Rheolytic thrombectomy

The AngioJet (Boston Scientific, Marlborough, USA) is a rheolytic thrombectomy device, made of a double-lumen over-the-wire catheter that uses the Bernoulli's principle for thrombus aspiration. The Bernoulli's principle states that for an inviscid flow of a non-conducting fluid, an increase in the speed of the fluid occurs simultaneously with a decrease in pressure. So, when the saline flow backwards at the tip of the catheter with a speed over 500 mph, a negative pressure is created which is responsible for aspiration.

The second lumen, with infusion apertures localized more proximally, delivers saline into the thrombus to fragment it and facilitate aspiration. The system requires that a complete thrombus passage is achieved to work appropriately, and at least a few passages are usually required to entirely clear the vessel.

The rapid stream of fluid and hydrodynamic forces used by thrombectomy devices may cause significant amount of red blood cell hemolysis resulting in hemoglobinemia and hemoglobinuria⁵⁸. This may occur when repeated passes of the device are required, resulting in severe consequences, mainly in patients with renal insufficiency.⁵⁹ The recommended maximum working time is limited to 300 s while working in the blood stream and 600 s within the thrombus, and it is highly suggested to hydrate the patient with isotonic saline during and after the procedure, to alkalize the urine with sodium bicarbonate and to utilize mannitol to maintain diuresis over 100 ml/hour after the procedure.

The AngioJet system has been tested in differ clinical scenarios: acute native thrombosis, thrombosed stents and surgical bypasses^{60,61}. Technical success with effective flow restoration was seen in 60 – 90 % of patients^{62,63}. The PEARL (PEripheral Use of AngioJet Rheolytic Thrombectomy with a variety of catheter Lengths) registry⁶⁴ reported results of rheolytic pharmacomechanical thrombectomy for the management of ALLI. Procedural success was achieved in 83% of 283 patients, with half of the procedures completed without the need for adjunctive CDT. At 12-month follow-up, amputation-free survival and freedom from mortality were 81% and 91%, respectively; 12-month freedom from bleeding requiring transfusion was 91%, and freedom from renal failure was 95%. Not surprisingly, subgroup analysis revealed better outcomes in patients without infrapopliteal involvement and those who underwent rheolytic thrombectomy without CDT.

As well as the above-mentioned intravascular haemolysis and acute renal insufficiency, there have been a series of possible complications related to the mechanism of action of the system, including: vessel injury and acute closure, stent graft collapse during thrombectomy⁶⁵, distal embolization and acute pancreatitis⁶⁶,

Aspiration thrombectomy

Aspiration thrombectomy is an alternative option for thrombus removal in patients with ALLI. It is feasible in patients with high risk of bleeding when thrombolysis is contraindicated (hepatic failure, recent surgery, trauma or a neurovascular accident), offering flow restoration in few minutes and not in hours as required by CDT. Moreover, there is no risk of haemolysis as reported after rheolytic thrombectomy.

Different devices have been available on the market up to now: in two of them, the Aspirex[®] thrombectomy system (Straub Medical AG, Wangs, Switzerland) and The ThromCat XT[®] (Spectranetics International, Leusden, The Netherlands) aspiration is associated with a rotational thrombectomy system; in one, the Indigo[®] System (Penumbra, Alameda, USA), aspiration the only mechanism of action.

The Aspirex is provided with a steel helix with a coaxial central lumen for a guidewire rotates inside a single-lumen rotational catheter with a speed of 40,000 – 60,000 rpm, producing negative pressure at the catheter tip. The thrombus is first aspirated, then fragmented by the spinning helix and transported to the collection bag. Although the spinning helix is located inside the catheter, it is advocated to avoid any contact with the vessel wall for the risk of injury.

The ThromCat XT[®] is a rotational thrombectomy catheter primarily developed for coronary interventions. Its flexible and atraumatic tip catheter consists of a stainless steel helix with a kink-resistant covering. The catheter neck encases the distal end of the helix, thus avoiding any direct contact with the vessel wall. Due to increased flexibility, it is suitable for crossover access. Although the device received CE mark approval in 2009, data on its efficacy are still limited. The technical success with a restoration of flow is reported in 70% of patients, with thrombus age (especially if greater than five days) as a major predictor of failure⁶⁷.

The Indigo system promotes active thrombectomy using a vacuum pump that generates substantial suction, enabling aspiration of clots of varying sizes and lengths. The device has three components: aspiration catheter, separator and pump. The system is not provided of any rotational components, and then the risk of vessel injury is truly minimized.

The Indigo represents a last generation system for thromboembolic disease, being designed specifically to address the limitations of conventional technology⁶⁸. Many of the first generation mechanical endovascular devices for thrombus removal have failed to be adequately successful or have been associated with unacceptable complication rates. The reasons have been mainly related to the limited trackability, the risk of vessel injury, and/or the incidence of incomplete revascularization. Actually, the engineer challenge is to design a dedicated device for lower limb arteries, which can remove adequate volumes of variable age thrombus while also maintaining an acceptably small size, flexibility, atraumatic tip and ease of use (fig. 3).

Since 2005, the Penumbra System became available in Europe and the United States for the revascularization of occluded intracranial vessels in patients with acute ischemic stroke. The Penumbra system used vacuum aspiration as its primary mechanism of action. A flexible, atraumatic large-bore catheter is delivered to the site of occlusion, and aspiration is directly applied to the lesion itself. To maintain lumen patency of the large-bore catheter, a Penumbra Separator[™] can be used at the tip of the catheter to continually break up the clot once ingested under aspiration. The Separator allows continuous thrombectomy under constant aspiration supplied by an external vacuum pump. The Pump MAX[™] is capable of delivering and maintaining nearly pure vacuum (98.2 kPa).

By demonstrating to be safe and effective in the neurovasculature and to provide high rates of complete intracranial vessels revascularization, the Penumbra system has began the market leader in stroke. Consequently, physicians who were familiar with the Penumbra system for stroke care started using it in the peripheral vasculature for acute thrombotic and embolic events. Lesions that were previously inaccessible with conventional technology, was then treated by these atraumatic, ultra-flexible neurovascular devices. In 2014, Penumbra launched the Indigo System specifically for this application, redefining below-the-knee mechanical thrombectomy. This is achieved by utilizing Penumbra's proprietary catheter-tracking technology and patented Separator technology for mechanical clot engagement. This percutaneous system is available in 8-F (three different tip shapes), 6-F, 5-F and 3-F catheter options (namely CAT 8 STR/TORQ/XTORQ, CAT 6, CAT 5, CAT 3). The Indigo has the largest extraction lumen

designed for vessels below the knee, with smaller and longer catheter options for hard-to-reach distal extremities. The catheter-tracking technology allows the device to reach the foot even from a contralateral approach (figure 4).

Although some very promising case report experiences, clinical data with this thrombectomy device in patients with ALLI is still limited. An on-going trial, called PRISM⁶⁹, has been designed to evaluate safety and efficacy of the Indigo® thrombectomy catheter. The examined population consists of ALLI patients with thrombolysis failure. Partial results were recently published, showing promising results with safe and effective mechanical thrombo-embolectomy in the peripheral arterial vasculature (technical success rate of 86.4%). These results were reached across a broad range of clinical applications including acute ischemia, removal of emboli that occurred during other endovascular procedures, and after failed thrombolysis.

CONCLUSION

Modifications in the treatment of ALLI have been proposed in recent years. While surgery represents still a significant treatment option especially for ALLI due to embolism, endovascular techniques are acquiring a more prominent role in case of acute on chronic ischemia. Various mechanical endovascular systems for thrombus removal have been investigated over the last 15 years. Most of them have partially failed to be effectively successful or have been associated with undesirable complication rates. New endovascular thrombectomy devices specifically designed for peripheral intervention in this difficult set of patients, may offer improved clinical outcomes with lower rates of major systemic and local complications. As a result, a shift of treatment recommendation towards endovascular options may be observed in the near future.

Figure Legends

Fig.1 Angiographic images of acute on chronic ischemia: a) arterial embolism to popliteal artery, b) arterial thrombosis occurring in the setting of preexisting occlusive disease with collateral arteries visualized.

Fig.2 a) Completion angiography after embolectomy by Fogarty demonstrate vessel injury with popliteal artery dissection); b) hybrid treatment with balloon angioplasty and stenting

Fig.3 a) Acute iliac stent thrombosis; b) Macroscopic aspect of thrombus removed by aspiration thrombectomy using Indigo CAT 8 XTORQ; c) Artery patency restored.

Fig. 4 a) Distal micro-embolism at level of tibial and plantar arteries; navigation with a Indigo CAT 3; b) Macroscopic aspect of thrombus removed by aspiration thrombectomy from posterior tibial and plantar arteries; c) Acute technical success result

Figure 1

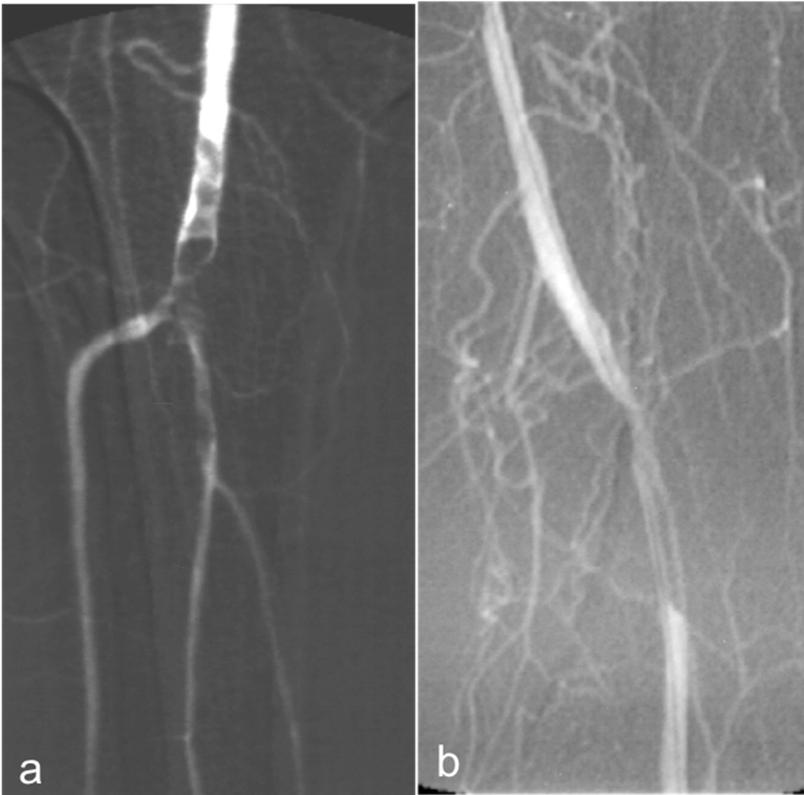


Figure 2

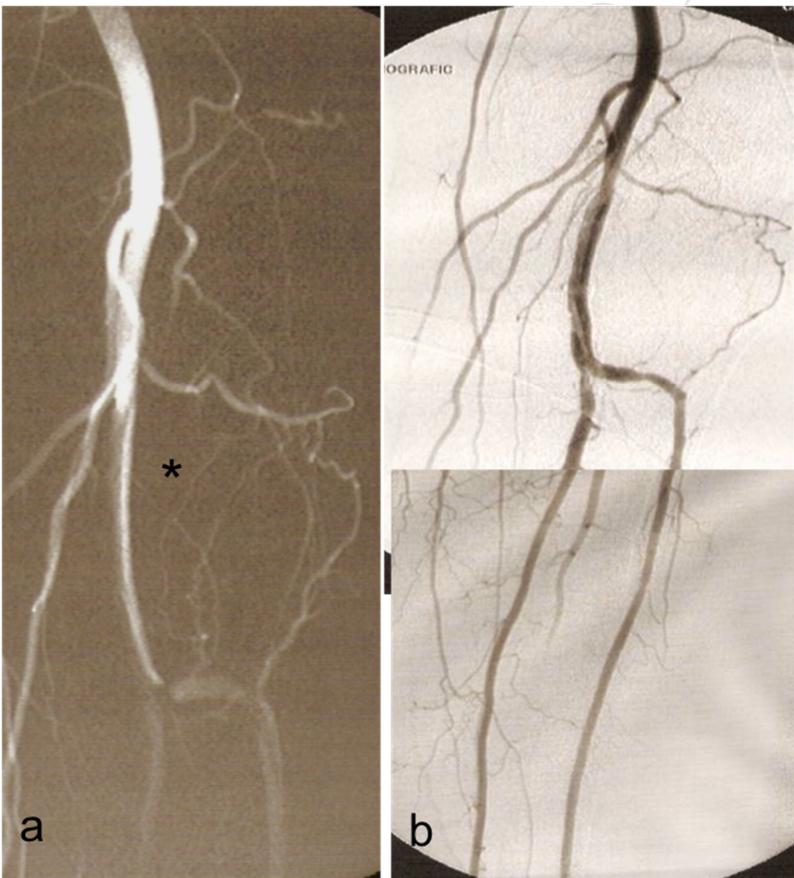


Figure 3

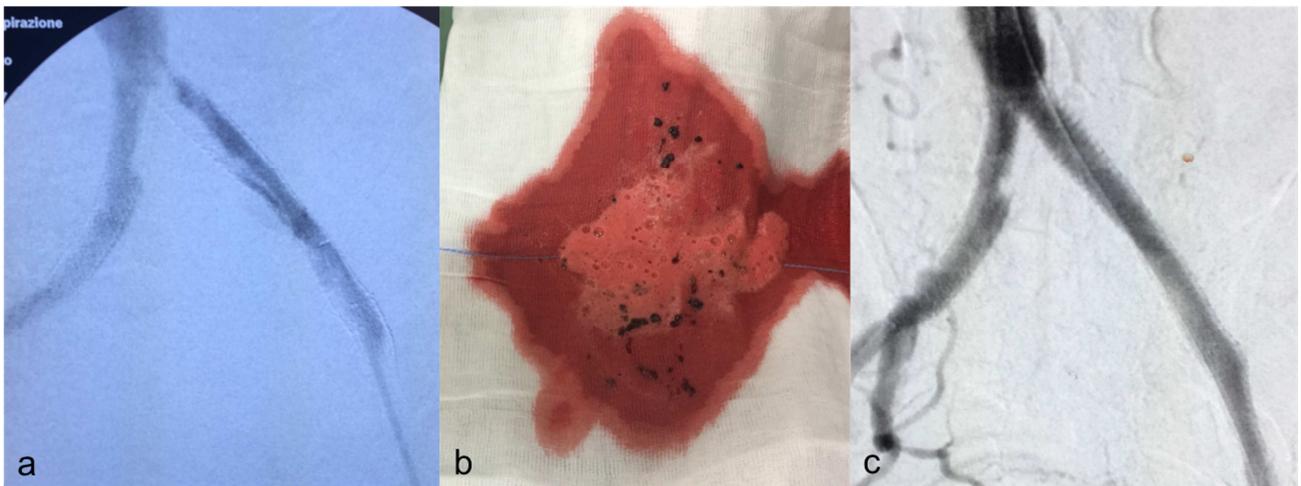
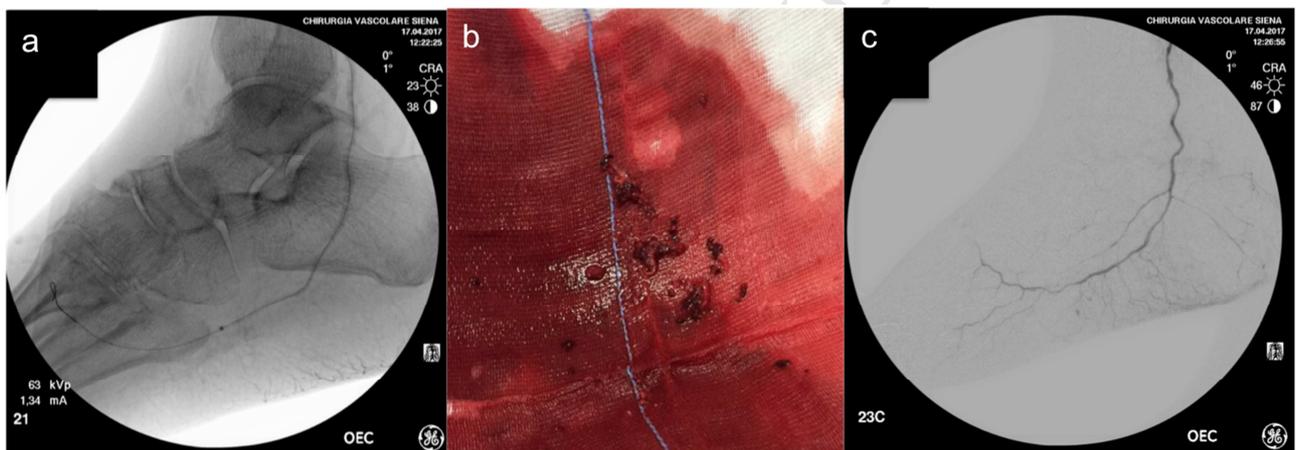


Figure 4



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