We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Acute Arterial Embolism of the Lower Limb

André Luís Foroni Casas

Abstract

Despite advances in the management of peripheral arterial occlusive disease, acute embolism of the lower extremities is still characterized by an important limb threat, morbidity, mortality, and continues to pose a challenge to the vascular surgeon. Atrial fibrillation, left ventricular aneurysm, penetrating ulcers or aneurysms of the aorta and common iliac arteries are the common sources of emboli. The presence of occlusion can be determined noninvasively with the use of duplex Doppler ultrasonography. Arteriography, Computed Tomographic Angiography and Magnetic Resonance Angiography can also be employed. Embolectomy is the standard for acute leg ischemia in patients with a strong clinical suspicion of an embolus, but alternative techniques, such as catheter-directed thrombolysis or percutaneous aspiration thrombolectomy, expand the role of radiologic percutaneous therapy of the acutely ischemic limb.

Keywords: thrombosis, embolism, embolectomy, fibrinolysis, lower extremity

1. Introduction

Acute limb ischemia results from a sudden decrease in limb perfusion that threatens limb viability and often requires urgent revascularization [1]. Acute ischemia of the lower limb continues to pose a challenge to the vascular surgeon and is still characterized by an important morbidity, limb threat and mortality. The two principal etiologies of acute ischemia of the lower limbs are arterial embolism and in situ thrombosis of an atherosclerotic artery or of a bypass graft [2]. It is estimated that the incidence of acute limb ischemia in the general population is around 14/100,000 inhabitants per year [3].

The consequences of acute limb ischemia such as prolonged hospitalization, major limb amputation, and/or death have a profound socioeconomic impact. Acute limb ischemia represents a high-risk cohort in need of complex revascularization procedures that are often associated with a significant rate of periinterventional complications [4]. Historic rates of amputation and mortality range from 10 to 25%, emphasizing the need for prompt evaluation and treatment [5, 6].

Embolism is the result of material passing through the arterial tree and obstructing a peripheral artery [7]. These materials may be thrombi, fragments of atheromatous plaque, tumor cells, or other foreign bodies, that have been dislodged or introduced into any part of the arterial system and can cause partial or total occlusion of an artery at a point distant from where they originated [8].

The arteries most commonly affected in the lower limbs are the femoral, the popliteal, the iliac, and the aorta [9–13]. The most frequent site of involvement is the femoral bifurcation, accounting for 35–50% of cases [14–17].

The approach of the arterial embolism of the lower limb has evolved significantly in the past decade, especially regarding the development of endovascular treatment.

2. Etiology

The heart has been described as a source of emboli with frequency in the range of 78–96% [12, 18]. When emboli originate in the heart, more than 70% will obstruct the lower limbs, including those lodged at the bifurcation of the aorta [19]. The majority of emboli originate in the heart, primarily the left heart, as a result of fragmentation of intracavitary thrombi [15, 16].

Atrial fibrillation, left ventricular aneurysm, penetrating ulcers or aneurysms of the aorta and common iliac arteries are the common sources of emboli. Nearly all emboli arise from the left heart, aorta, and iliac vessels. A minority are paradoxical venous emboli that pass through an intracardiac shunt. Emboli typically lodge at branch points in the vascular tree and occlude both tributaries [20]. The most frequent cause of formation of these thrombi is atrial fibrillation, which occurs in mitral valve lesions of rheumatic origin, hyperthyroidism, acute myocardial infarction, and cardiosclerosis. The hemodynamic changes caused by atrial fibrillation, causing formation of mural thrombi, is the most important source of emboli [16, 21]. Autopsy studies of heart patients with and without atrial fibrillation showed that the frequency was much higher in the first group [22].

The most frequent cause of emboli among the valve disorders is mitral valve disease, primarily mitral stenosis of rheumatic origin. Thrombi may develop in the subvalvar area, but frequency is greater in the left atrium. Among these patients, two factors appear to be intimately linked with the embolic episode: age and presence of atrial fibrillation [21]. In the past, cardiac valve disease was the main cause of arterial embolism, but advances in the management of these patients have virtually eliminated this as a cause [23–25].

Patients with transmural myocardial infarction are at risk of embolization for 3–4 weeks after the acute event. The majority of these thrombi form in the left ventricle (the region most often involved in myocardial infarctions). Systemic embolization can occur after 5% of after acute myocardial infarction cases [17]. In patients with heart failure, the left atrium or the left ventricle may form thrombi, causing systemic emboli [8].

Another cause of emboli is intracardiac tumors. The tissue of these tumors may dislodge from the heart, causing distal emboli [26].

Acute or subacute bacterial endocarditis can cause arterial emboli, from deposits built up on the valve itself, or by encouraging formation of thrombi. In these cases, the arteries obstructed are generally those of narrower caliber [27].

Nowadays, invasive diagnostic, therapeutic procedures and cardiovascular surgery constitute an important iatrogenic source of peripheral emboli [28, 29]. Thromboembolic complications, including systemic emboli, occur at a rate of 0.7–6% patient-years in thrombosis of mechanical valves [30].

While rare, it is possible for a venous embolus to reach the arterial circulation, causing acute arterial occlusion (paradoxical embolism). In such cases, a thrombus with origin in peripheral veins crosses over to the arterial circulation when the patient has a persistent foramen ovale or intracardiac shunt or there is reversal of the pressure gradients between right and left heart chambers [31].

Cholesterol embolization syndrome (atheroembolism) refers to embolization of the contents of an atherosclerotic plaque (primarily cholesterol crystals) from a proximal large-caliber artery to distal small to medium arteries causing end-organ damage by mechanical plugging and an inflammatory response [32]. Embolization of cholesterol crystals from ulcerated atherosclerotic plaques is well known. Disseminated cholesterol emboli may produce a systemic illness with livedo reticularis of the lower limbs and splinter hemorrhages of the nails [33]. Atheroembolism leads to multifocal ischemic lesions and progressive tissue loss [34] (**Figure 1**). It occurs predominantly in elderly men with a history of atherosclerotic disease and hypertension [35]. Lesions of differing ages were found in individual cases, suggesting that the process of embolism was recurrent [33]. They can occur spontaneously, but are more common after trauma, endovascular procedures, open vascular surgery, thrombolysis, and anticoagulation [36, 37]. Extra-cardiac emboli are very often associated with aortic, iliac, femoral, and popliteal aneurysms. They occur in 5–10% of cases [38].

Tissues' resistance to anoxia is dependent on several factors, which includes metabolic requirements and the effectiveness of collateral circulation [39]. The peripheral nervous system is affected first [40], and therefore loss of sensation is one of the earliest signs of acute leg ischemia [7], the skeletal musculature is affected soon afterwards, and irreversible damage can occur after 6 h of ischemia. The skin, subcutaneous tissue, bone tissues, and cartilage have greater resistance to ischemia [40]. This is why muscle tenderness is one of the end-stage signs of acute leg ischemia [7] **Table 1** shows the lower limb emboli sources.



Figure 1.
Atheroembolism.

Cardiac
1. Atrial fibrillation
2. Left ventricular aneurysm
3. Intracardiac shunt
4. Valve disorders
5. Myocardial infarction
6. Heart failure
7. Intracardiac tumors
8. Endocarditis
Extracardiac
1. Aorta-iliac penetrating ulcers
2. Aneurysms of the aorta, iliac, femoral, and popliteal arteries
3. Iatrogenic (invasive diagnostic, therapeutic procedures, cardiovascular surgery, thrombolysis and anticoagulation)
4. Cholesterol embolization syndrome (atheroembolism)
5. Trauma

Table 1.
Lower limb emboli sources.

3. Clinical assessment

The symptoms caused by vascular occlusion depend on the size of the artery occluded and whether collaterals have developed beforehand [7]. The classic description of acute occlusion of a lower limb artery is of acute pain with sudden onset, cyanosis, paresthesia, paralysis, cold, pallor, and absent pulses distal to the site of occlusion (**Figure 2**). The symptoms of paresis, hypoesthesia, or even paralysis are related to ischemic damage to nerve fibers. The segment distal to the occlusion will exhibit pallor of variable extent and intensity, intensifying when the limb is raised. In the majority of cases of acute arterial occlusion, pulses distal of the site of occlusion are absent, but in rare cases they may be present because of collateral circulation. In this patients, onset of pain may be more insidious and pain may be less intense [8]. Therefore, sudden occlusion of a proximal artery without existing collaterals leads to an acute white leg, whereas occlusion of the superficial femoral artery in the presence of well-established collaterals may be asymptomatic [7].

Handheld Doppler examination is also a basic part of the examination. The presence of normal biphasic signals excludes the diagnosis. Pedal arterial signals may be absent or reduced. Soft monophasic signals are associated with patent distal vessels but proximal arterial occlusion. Absent Doppler signals in the ankle arteries is a poor prognostic sign. In severe ischemia, ankle Doppler pressures are impossible to measure. In patients



Figure 2.
Clinical assessment of acute arterial embolism of the lower limb.

Category	Description/prognosis	Findings		Doppler signals	
		Sensory loss	Muscle weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitables	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Table 2.
Clinical categories of acute limb ischemia.

with severe ischemia, irreversible muscle necrosis occurs within 6 h if the condition is untreated [7]. The severity of limb ischemia at the time of admission to the hospital seems to be a more important factor in limb salvage than the time interval between embolic episode and operation. Even after long delay, if the limb appears to be viable on examination, the probability exists for a successful operation. This is due to adequate collateral circulation supplying the extremity until the blockage is removed [41].

It is difficult to determine by clinical examination the limits of reversibility of lower limb ischemia. Tissue viability tests should be performed. Rutherford et al. [42], proposed a clinical classification of acute limb ischemia comprising 3 groups in an attempt to establish parameters to define treatment (**Table 2**). Three general classes are recognized:

Class I: Non-threatened extremity; elective revascularization may or may not be necessary.

Class II: Threatened extremity; revascularization is indicated to prevent tissue loss.

Class III: Ischemia has progressed to infarction and salvage of the extremity is not possible.

The most lethal form of acute arterial embolism is emboli of the aortic bifurcation, with symptoms in both lower limbs and in some cases spinal ischemia caused by involvement of lumbar arteries [43].

4. Complementary exams

When time permits, some methods can be used to definitively determine the site and nature of the arterial occlusion. Investigation may be valuable in confirming the clinical diagnosis and planning the treatment for patients with acute ischemia. The modern treatment in a hybrid operating room with access to the full range of surgical and interventional procedures is the best approach. Unfortunately, sometimes there may be no time for investigation [7].

4.1 Ultrasound

The Doppler Ultrasound exam can be employed in cases of acute ischemia to define the level of the arterial occlusion and the patency of other vessels [7]. It can

also provide information that confirms diagnosis and occasionally reveals concurrent venous thrombosis. Detection of distal flow at pressures exceeding 50 mmHg confirms significant collateral circulation, demonstrating that additional time is available to conduct a more thorough evaluation of the case [8]. Portable ultrasound machines may permit rapid, bedside imaging by vascular specialists trained in duplex imaging [7].

4.2 Computed tomographic angiography (CTA)

CTA has become the exam of choice for urgent investigation of acute arterial ischemia [7]. It provides good quality images, offering the possibility of three-dimensional reconstruction, and is of similar quality to angiography [8] (**Figure 3**). A new-generation computed tomography scanners acquire images at very high speed and are available in most emergency suites. The images sometimes require manipulation to produce the best results. These images are particularly good for aortoiliac occlusions but give adequate information to plan treatment of infrainguinal occlusions [7]. It has the disadvantage of using iodine contrast, which restricts use of this examination with patients allergic to iodine or with pre-dialysis chronic stage of renal insufficiency [8]. In these cases, intravenous fluids should be considered for prehydration [7].

4.3 Arteriography

Arteriography was the mainstay of investigation for acute leg ischemia, but it is less accessible than CT angiography in many hospitals without a hybrid operation room [7]. It should be chosen in selected cases with viable extremities, in which it will not delay treatment. Immediately threatened patients should undergo

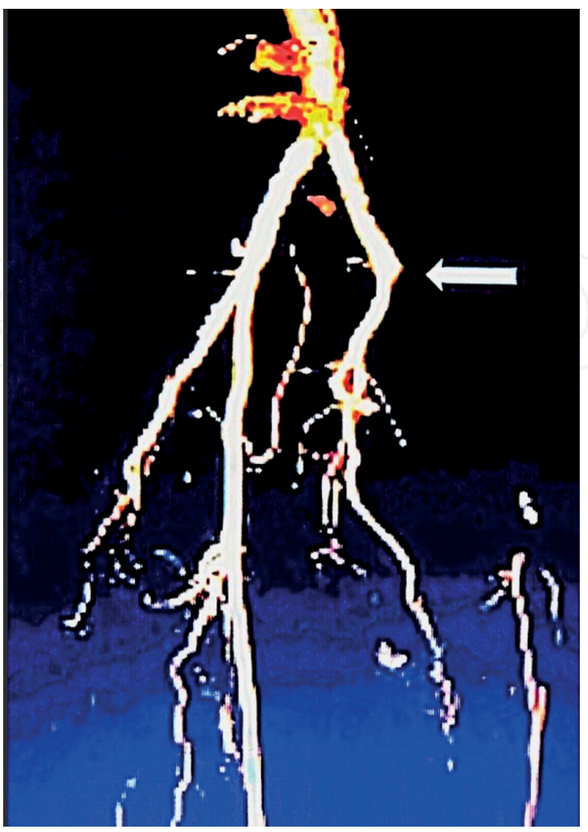


Figure 3.
Angiotomography demonstrating acute arterial embolism in the origin of the left external iliac artery (arrow).

embolectomy at once, conducting arteriography intraoperatively. This examination can reveal the embolic or thrombotic nature of the obstruction in a large number of cases [8]. Brachial puncture can be used in the absence of femoral pulses. The arteriography documents the level of occlusion and sometimes its nature. Sometimes emboli can be seen in several vessels, establishing the diagnosis.

Arteriography may not visualize all the distal vessels in the acute situation, because the lack of collaterals and associated spasm limit visualization. Angiography is the best choice when an endovascular solution to the arterial occlusion is likely, because thrombolysis, percutaneous thrombectomy, angioplasty, or stenting can be performed during the same operative session. It may still be worth exploring distal vessels surgically when contemplating a distal bypass in this situation [7].

There are angiographic signs suggestive of emboli: a filling defect at the level of the occlusion, normal artery wall, poor or absent collateral circulation, and occlusive involvement at bifurcations [8].

4.4 Magnetic resonance angiography (MRI)

It has not yet fully established the point MRI can be used to substitute conventional angiography (which remains the gold standard diagnostic examination) or angiotomography, which offers better results in cases with calcified atherosclerotic plaque [8]. MRI has the advantage to produce an image, without the need of ionizing radiation or nephrotoxic contrast agents [44].

Magnetic resonance angiography with gadolinium is less useful than either CT or ultrasound in the acute limb ischemia. It takes time to acquire images, and is generally inconvenient [7].

4.5 Echocardiography

The echocardiography can be omitted when a cardiac source of embolism appears from the clinical setting [45]. In practical terms, the investigation rarely alters management, because most patients are anticoagulated for life after successful treatment for acute ischemia. There are certainly some conditions that require echocardiography to make a diagnosis, such as valvular disease (including vegetations), septal defect, and cardiac tumor. Problems associated with the routine application of echocardiography include the variability in results between transthoracic and transesophageal techniques, the inability to visualize the left atrial appendage, the fact that failure to visualize the source of an embolus does not rule out its existence, and the test's lack of influence on overall management [46]. A practical view would be that echocardiography is indicated in young patients, those in whom a cardiac diagnosis is suspected, and those in whom the results might affect decisions about long-term anticoagulation [7].

4.6 Laboratory tests

Muscle ischemia is accompanied by a considerable increase in creatine phosphokinase (CPK). The elevation is so marked that for a long time it was considered that CPK level was a determinant of the degree of ischemia and of prognosis of recovery of the ischemic limb after revascularization. The level of leukocytes in circulation may also increase [47]. LDH and SGOT levels are also increased in cases of acute arterial occlusion, because of the ischemic insult to skeletal musculature. Some authors recommend testing levels of LDH, CPK and their respective isozymes in these patients [48, 49].

5. Treatment

Once the initial assessment is complete, a decision should be made about the intervention required and its timing. The threat to the limb escalates with secondary thrombosis of underperfused distal vessels, particularly in patients with emboli. The following options are available: anticoagulation alone, operative intervention, and endovascular intervention via mechanical thrombectomy or thrombolysis [7]. A distinction between subacute (class I) and true limb-threatening ischemia (classes IIa, IIb and III) becomes relevant regarding the urgency of care and risk of limb loss [50].

The choice of intervention depends on the available expertise and the severity of the leg ischemia [1]. There is a suggestion that endovascular first treatment may be more expensive overall [51], but even in modern series, open vascular reconstruction for acute limb ischemia carries a significant risk of major morbidity (20%) or limb loss (22%) [52].

5.1 Auxiliary measures

In patients with there is risk of renal dysfunction, so an intravenous infusion of fluid is appropriate [7]. Other first-aid measures that are beneficial in patients with leg ischemia include the use of oxygen. This has been shown to improve skin perfusion, even in the ischemic limb [53]. A blood sample is indicated. In patients with recurrent thrombosis, a full thrombophilia screen should be performed at this stage [54, 55]. These tests are indicated in patients with a strong family history of arterial and venous thrombosis or those with recurrent disease [56, 57]. Analgesics and sedatives are also employed for pain relief [8].

5.2 Anticoagulation

Heparin should be administered as soon as possible when the acute arterial occlusion has been diagnosed. This drug prevents secondary thrombosis and venous thrombosis that may be present from advancing, both of which are factors that worsen prognosis [58, 59]. Use of anticoagulation alone as a treatment implies that the limb is likely to remain viable or that other therapeutic options are limited, perhaps by age or comorbidity. The anticoagulants made an immediate impact in the morbidity and mortality rates after their introduction [60, 61].

Whereas low-molecular-weight heparin is a valuable therapy for many conditions, the potential for reversal with protamine makes calcium heparin the drug of choice in this situation [7]. The majority of authors recommend intravenous administration of calcium heparin in bolus at a dosage of 5000–10,000 units [58, 59]. In patients in whom definitive treatment is deferred an intravenous heparin infusion (18 U/kg/h) should be prescribed [62].

5.3 Thromboembolectomy

After Fogarty et al. described the embolectomy catheter for the remote removal of a clot via a groin incision in 1963, surgery became the main treatment for acute leg ischemia [63]. The arterial thromboembolectomy is an efficient treatment for acute arterial thromboemboli of lower limbs, especially if a single large artery is involved. Unfortunately, residual thrombus, propagation of thrombi, chronic atherosclerotic disease, and vessel injuries secondary to balloon catheter passage may limit the clinical success rate [64].

While the time elapsed between the embolic episode and effective treatment is an important prognostic factor, experience has shown that good results can still be achieved even with late thromboembolectomy, as long as the limb is viable [11, 65]. The most appropriate access for aortoiliac, femoral, popliteal emboli is the common femoral artery at the femoral triangle (bilaterally for emboli of the aorta) [17] (**Figure 4**). Embolectomy is less likely to be effective for distal occlusions [8].

The benefits of open surgical embolectomy are rapid restoration of blood flow and the ease of the procedure, whereas the risks include a greater physiological stress and concomitant blood loss [50].

5.4 Thrombolysis

Unlike surgical embolectomy, thrombolysis lyses clot in both large and small arteries and arteriolar and capillary beds [66].

Low dose intra-arterial fibrinolytic therapy treatment has its place as an alternative to surgical treatment of acute embolic occlusions in selected cases [67, 68]. The recommendation for intra-arterial thrombolysis is applicable to patients with embolic acute arterial occlusion of less than 14 days duration and with sufficient collateral circulation to maintain limb viability for 12 h [69, 70].

Currently available agents include alteplase (rt-PA), reteplase (rPA), and tenecteplase (TNK). The bolus is delivery of a single concentrated dose of thrombolytic agent throughout the occlusion and then the continuous infusion is initiated. Pulse spray refers to repeated forceful injection of thrombolytic, thus distributing the agent rapidly throughout the thrombus.

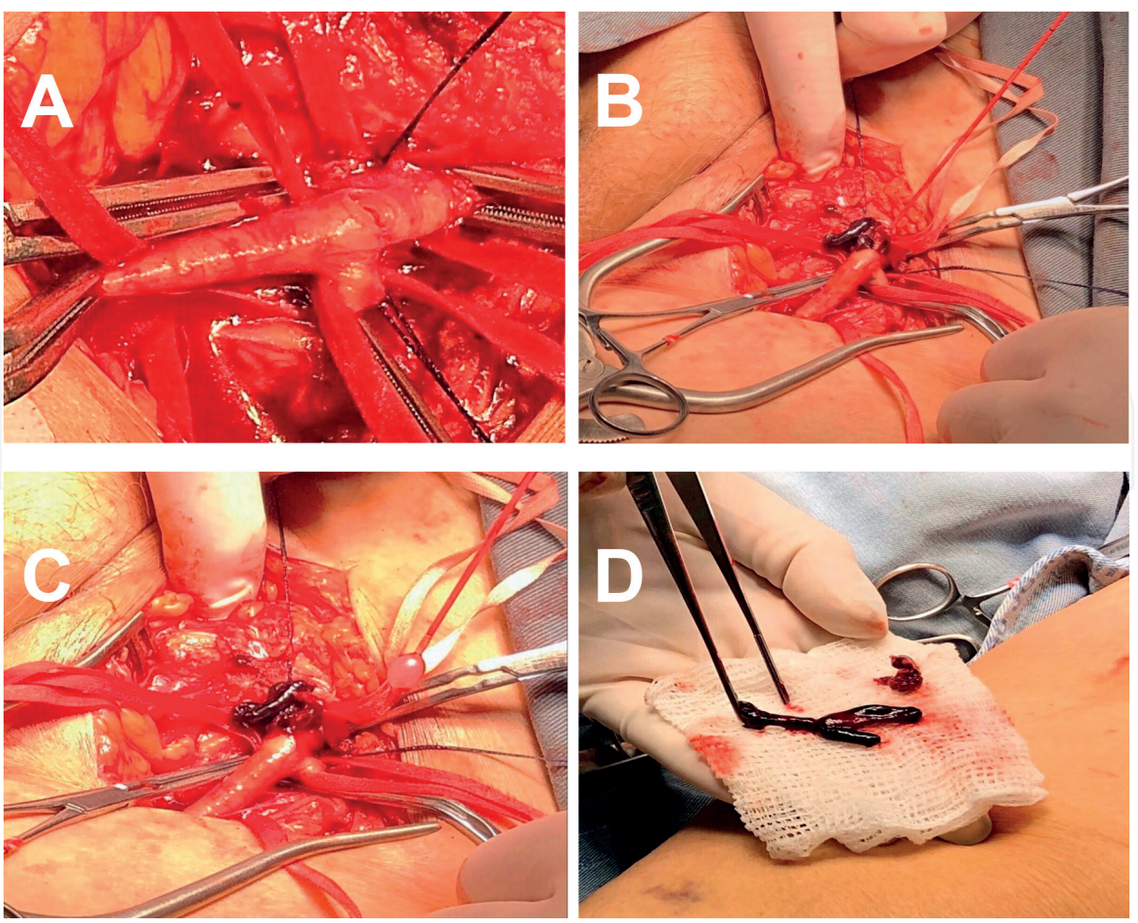


Figure 4.
Embolectomy in lower limb: (A) exposure of the femoral arteries and arteriotomy; (B and C) introduction of the Fogarty catheter for thrombus removal; and (D) thrombi removed from the arterial system.

The commonly used doses today are Alteplase (rt-PA): continuous, 0.5–1.0 mg/kg/h (40 mg maximum); bolus, 2–5 mg bolus, then continuous infusion; pulse spray, 0.5 mg/mL at 0.2 mL every 30–60 seconds, Reteplase (rPA): continuous, 0.25–0.5 U/h (20 units maximum); bolus, 2–5 U bolus, then continuous infusion and Tenecteplase (TNK): continuous, 0.125–0.25 mg/h; bolus, 1–5 mg, then continuous infusion (20).

Streptokinase, the first-generation agent, is still used in some centers. This drug is used intra-arterially, by continuous infusion through a multiperforated catheter, positioned immediately before the obstruction, with release of the thrombolytic inside the thrombus, activating plasminogen bound to it [71]. This technique made it possible to use streptokinase at much lower doses, reducing the risk of hemorrhage, while maintaining its thrombolytic power. The dose used is 5000 UI/h, controlling coagulation status every 12 h by fibrinogen assay, TP, and TTPA, attempting not to allow fibrinogen to fall below 100 mg%. Good results are achieved using this technique [72–74], although there are hemorrhagic complications in up to 20% of cases [59]. The infusion is then maintained at a dosage of 1 mg/h and the patient is kept anticoagulated with unfractionated heparin on a continuous infusion pump [8]. Heparin can be infused intravenously or intra-arterially through the sheath. A bolus at the time of thrombolysis initiation is not recommended. An infusion rate to raise PTT to only 1.25–1.5 of control is recommended. Most practitioners use between 200 and 500 U/h [20].

Some prospective and randomized studies compared direct thrombolysis with surgical revascularization in cases of acute arterial occlusion and the two approaches were not different for limb salvage or mortality, but fibrinolysis was associated with a higher risk of hemorrhagic events [66, 75–77].

5.4.1 Contraindications to thrombolytic therapy

Many patients with acute limb ischemia are not candidates for thrombolysis because of excessive major bleeding risks. All major and minor contraindications should be viewed in the context of the clinical circumstance. The increased risk of bleeding complications may be assumed if the alternative is likely limb loss or death [20]. **Table 3** lists thrombolytics contraindications [78].

When using thrombolytics, arteriography should be performed every 6 h, or in the event of changes to the patient's clinical. Fibrinogen assay also should be performed every 6 h. If the results of these tests are undesirable, fibrinolytic agent should be suspended [8].

The criteria for successful thrombolysis are radiological evidence of lysis with arterial recanalization at least as far as the next major collateral, an increase in the ankle brachial index greater than or equal to 0.2, limb salvage at 30 days without recourse to reconstructive surgery at the level at which lysis was performed and no clinical evidence or rethrombosis within the first 30 days [79].

5.5 Percutaneous aspiration thrombectomy

The treatment of the arterial embolism of the lower limb has evolved significantly, especially regarding the development of endovascular devices.

Percutaneous aspiration thrombectomy is another resource that offers and is an alternative to surgical treatment and can be combined with angioplasty or fibrinolytic therapy [80, 81]. These materials generally employ simple mechanisms for aspiration or destruction of the thrombus [82].

Promising results were obtained for percutaneous mechanical thrombectomy, employing a range of different equipment [81, 83–86]. The trend is that endovascular treatment significantly evolves, with the development of new and less invasive of these devices.

Absolute
1. Established cerebrovascular event (including transient ischemic attacks within last 2 months)
2. Active bleeding diathesis
3. Recent gastrointestinal bleeding (<10 days)
4. Neurosurgery (intracranial, spinal) within last 3 months
5. Intracranial trauma within last 3 months
Relative major
1. Cardiopulmonary resuscitation within last 10 days
2. Major nonvascular surgery or trauma within last 10 days
3. Uncontrolled hypertension: >180 mmHg systolic or >110 mmHg diastolic
4. Puncture of noncompressible vessel
5. Intracranial tumor
6. Recent eye surgery
Minor
1. Hepatic failure, particularly those with coagulopathy
2. Bacterial endocarditis
3. Pregnancy
4. Diabetic hemorrhagic retinopathy

Table 3.
Thrombolysis contraindications.

6. Postoperative anticoagulation

Postoperative anticoagulation is recommended long term and, sometimes, even indefinitely, in cases of atrial fibrillation and arterial emboli in which the source of origin is not identified or is not controlled [11]. One study demonstrated 31% recurrence of emboli in patients not taking anticoagulants during the postoperative period vs. 9% among those taking anticoagulants [16].

New drugs are currently used for postoperative anticoagulation, mainly factor Xa inhibitors. There are evidences to justify its use, in order to prevent recurrent episodes.

7. Postoperative complications

High operative mortality among patients suffering from acute ischemia is a well-established observation. Both serious cardiac disease and reperfusion injury contribute to mortality [87].

Mortality from acute arterial occlusion are reported from 7 to 37% and the amputation rate in patients with embolism 10–30% [88, 89].

Acute myocardial infarction and arrhythmia are responsible for the majority of deaths and, despite advances in technology and clinical support, mortality among acute arterial occlusion patients remains high [8], particularly among the elderly [90]. One study demonstrated that New York Heart Association (NYHA) classification was the most important predictor for survival (class 3–4 had a 3.35 times higher death rate than class 1–2) [91]. Advanced age, recent myocardial infarction and proximal occlusions are also associated with a high mortality rate after arterial thromboembolectomy [92].

7.1 Compartment syndrome

After limb revascularization (particularly if ischemia is intense and prolonged) compartment syndrome may occur. This is due to edema increasing the pressure

in muscle compartments situated between inelastic fascia and bones, which can compromise tissue perfusion. It may be caused by a chain of events secondary to ischemia-reperfusion, including with release of thromboxane A2 [8]. The ischemia-reperfusion phenomenon plays an important role in the pathogenesis of compartment syndrome due. Ischemia-reperfusion increases compartment volume by causing muscle tissue injury, which leads to increased microvascular permeability, with efflux of plasma proteins and progressive interstitial edema [93]. With reperfusion, oxygen radical generation exacerbates microvascular permeability and resulting interstitial edema [94].

For diagnosis, some authors describe tissue pressures exceeding 30–45 mmHg [95, 96]. However, there are also authors who recommend diagnosis based on clinical criteria alone (spontaneous pain, pain on flexion or passive extension of the foot, tense edema, hypoperfusion, missing pulse, paresthesia, anesthesia, paresis, or paralysis) [8]. Risk factors for compartment syndrome after acute arterial ischemia includes prolonged ischemia time, young age, insufficient arterial collaterals, acute time course for arterial occlusion, hypotension and poor back-bleeding from the distal arterial tree at embolectomy [94].

Once a diagnosis of compartment syndrome has been made, fasciotomy should be conducted promptly, since it releases muscle compression, reestablishes capillary blood flow, and restores the caliber of arteries e veins. In general, this procedure is associated with low morbidity. The staged fasciotomy technique is generally sufficient to decompress the anterior and posterior compartments. If this does not provide sufficient relief of compression, 4-compartment fasciotomy should be performed via a wide incision. Incisions can be sutured after 1–2 weeks or heal by secondary intention [8].

7.2 Ischemia: reperfusion injury

This primarily occurs after ischemia of large muscle masses, which can develop local and systemic metabolic abnormalities after arterial desobstruction and reperfusion of ischemic tissues [97]. One study demonstrated a 7.5% incidence of this syndrome in patients with acute arterial occlusion, with 4.7% mortality [98].

Serious metabolic abnormalities can develop with ischemia of the lower limb muscle mass [99]. Ischemia compromises the integrity of the cell membrane and cause cellular dysfunction [100–102]. The reperfusion can exacerbate it, making the damage irreversible [103].

Tissue hypoxia results in movement of neutrophils and macrophages into the interstitium through the action of hypoxia adaptive pathways [104–106]. Activated neutrophils subsequently release molecular mediators, which contribute to the production of adenosine on the vascular endothelial surface, a protective factor that restores endothelial integrity [107, 108]. Activated leukocytes also have significant pro-inflammatory consequences. Neutrophils release factors that increase endothelial permeability and cytoskeletal rearrangement [109].

During ischemia, the supply of oxygen to cells is reduced, decreasing aerobic metabolism and, consequently, reducing the energy available for maintenance of cellular metabolism [110]. In consequence of the reduced energy supply, the sodium-potassium-ATPase protein is affected and the sodium and potassium pump fails, resulting in cellular edema and ion flow disorders [111].

Oxygen free radicals are produced by molecular oxygen reintroduced into the ischemic tissue during reperfusion [102]. They can cause cell injury by reacting with polysaturated fatty acids, leading to peroxidation of lipid components in the membrane [112], which can rupture cell integrity [102] and attract leukocytes to the ischemic tissues. Reperfusion of ischemic tissue can have effects that are highly damaging to the

function of distant organs [113]. Data are emerging regarding the important role of the tumor necrosis factor-α (TNF-α), released from activated macrophages [114].

Serious pulmonary injuries, such as low oxygen tension, pulmonary edema, pulmonary hypertension and inflammatory response, can be caused by the activity of mediators such as free oxygen radicals, thromboxane, leukotrienes and neutrophils [115, 116].

Serum potassium levels can vary after revascularization. Hyperkalemia is a consequence of myocytolysis and, in combination with acidosis, can lead to myocardial depression, hypotension, arrhythmia, and cardiac arrest. Renal dysfunction may occur, depending on the degree of metabolic acidosis, muscle injury, myoglobinuria and hypovolemia [117, 118].

Adjuvants measures can be useful to attenuate or avoid additional damage to cells during the reperfusion period. These measures include hypothermia, controlled reperfusion, and hemodilution [119]. In some cases, it can be useful to drain the effluent blood from the limb, immediately after revascularization, with the objective of removing toxic products that have built up during the period of ischemia [18]. Free radical scavengers still need to be further evaluated for their efficacy for reducing post-reperfusion cellular damage [120]. There is evidence that antioxidant vitamins and calcium channel blockers could be useful for attenuating ischemia-reperfusion cell damage [121]. Preventative measures for ischemia-reperfusion syndrome are alkalinization, osmotic diuresis and correction of hyperkalemia. Red blood cells can be washed, resuspended, and reinfused [122, 123], primarily in cases with muscle rigidity [122].

8. Future avenues/developments

Advances in this area are evident. For many years, there was no specific treatment for lower limb embolism. The most serious cases were treated only with analgesia and amputation. The Fogarty catheter revolutionized the prognosis of these patients. Now, ever-greater advances are made, and even less invasive treatments gain space.

The tendency is that endovascular treatment, including fibrinolysis and percutaneous aspiration, evolves more and more, with the development of new and less invasive devices, and will probably be considered the treatment of choice for embolic occlusion of the lower limb.

9. Conclusion

Acute limb ischemia of the lower extremity is a potentially devastating condition that requires urgent and definitive management. The two principal etiologies of acute ischemia of the lower limbs are arterial embolism and in situ thrombosis of an atherosclerotic artery.

Despite major advances in the contemporary management of peripheral arterial occlusive disease, acute ischemia of the lower limb is still characterized by an important morbidity, limb threat, mortality, and continues to pose a challenge to the vascular surgeon.

Atrial fibrillation, left ventricular aneurysm, penetrating ulcers or aneurysms of the aorta and common iliac arteries are the common sources of emboli. The presence of occlusion can be determined noninvasively with the use of duplex Doppler ultrasonography. If time permits, Arteriography, Computed Tomographic Angiography and Magnetic Resonance Angiography can also be employed.

Embolectomy is the standard procedure for acute leg ischemia, mainly in patients with a strong clinical suspicion of an embolus, but alternative techniques, such as catheter-directed thrombolysis or percutaneous aspiration thrombolectomy, expand the role of radiologic percutaneous therapy of the acutely ischemic limb.

The worse consequences of acute limb ischemia are prolonged hospitalization, major limb amputation, and death, so prevention strategies should be aimed to avoid the episode.

Conflict of interest

The author has no conflicts of interest to disclose.

Author details

André Luís Foroni Casas
Universidade de Franca, Franca, SP, Brazil

*Address all correspondence to: vascular@andrecasas.com

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. The New England Journal of Medicine. 2012;**366**:2198-2206. DOI: 10.1056/NEJMcp1006054

[2] Van DH, Boesmans E, Defraigne JO. Acute limb ischemia. Revue Médicale de Liège. 2018;**73**:304-311

[3] Dormandy J, Heeck L, Vig S. Acute limb ischemia. Seminars in Vascular Surgery. 1999;**12**:148-153

[4] Kronlage M, Printz I, Vogel B, Blessing E, Muller OJ, Katus HA, et al. A comparative study on endovascular treatment of (sub)acute critical limb ischemia: Mechanical thrombectomy vs thrombolysis. Drug Design, Development and Therapy. 2017;**11**: 1233-1241. DOI: 10.2147/DDDT.S131503

[5] Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). Journal of Vascular Surgery. 2007;**45**(Suppl S):S5-S67. DOI: 10.1016/j.jvs.2006.12.037

[6] Karnabatidis D, Spiliopoulos S, Tsetis D, Siablis D. Quality improvement guidelines for percutaneous catheter-directed intra-arterial thrombolysis and mechanical thrombectomy for acute lower-limb ischemia. Cardiovascular and Interventional Radiology. 2011;**34**:1123-1136. DOI: 10.1007/s00270-011-0258-z

[7] Sidawy AN, Perler BA. Rutherford's Vascular Surgery and Endovascular Therapy. 9th ed. New York: Elsevier; 2018. p. 2832

[8] Maffei FHA, Yoshida WB, Rollo HA, Moura R, Sobreira ML, Giannini M, et al. Doenças Vasculares Periféricas. 5th ed. Vol. 2015. Rio de Janeiro: Guanabara Koogan. p. 2368

[9] Blaisdell FW. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: A review. Cardiovascular Surgery. 2002;**10**:620-630. DOI: 10.1177/096721090201000620

[10] Andersen LV, Lip GY, Lindholt JS, Frost L. Upper limb arterial thromboembolism: A systematic review on incidence, risk factors, and prognosis, including a meta-analysis of risk-modifying drugs. Journal of Thrombosis and Haemostasis. 2013;**11**:836-844. DOI: 10.1111/jth.12181

[11] Elliott JP Jr, Hageman JH, Szilagyi E, Ramakrishnan V, Bravo JJ, Smith RF. Arterial embolization: Problems of source, multiplicity, recurrence, and delayed treatment. Surgery. 1980;**88**:833-845

[12] Hight DW, Tilney N, Couch NP. Changing clinical trends in patients with peripheral arterial emboli. Surgery. 1976;**79**:172-176

[13] MacGowan WA, Mooneeram R. A review of 174 patients with arterial embolism. The British Journal of Surgery. 1973;**60**:894-898. DOI: 10.1002/bjs.1800601115

[14] Dale WA. Differential management of acute peripheral arterial ischemia. Journal of Vascular Surgery. 1984;**1**:269-278. DOI: 10.1016/0741-5214(84)90058-2

[15] Fogarty TJ, Daily PO, Shumway NE, Krippaehne W. Experience with balloon catheter technic for arterial embolectomy. American Journal of Surgery. 1971;**122**:231-237. DOI: 10.1016/0002-9610(71)90323-0

[16] Green RM, DeWeese JA, Rob CG. Arterial embolectomy before and after the Fogarty catheter. Surgery. 1975;**77**:24-33

[17] Panetta T, Thompson JE, Talkington CM, Garrett WV, Smith BL. Arterial embolectomy: A 34-year experience with 400 cases. The Surgical Clinics of North America. 1986;**66**:339-353. DOI: 10.1016/S0039-6109(16)43886-7

[18] Chin AK, Fogarty TJ. Management of arterial emboli. Gleanings from 20 years of experience. Postgraduate Medicine. 1987;**81**:271-276. DOI: 10.1080/00325481.1987.11699833

[19] Connett MC, Murray DH Jr, Wenneker WW. Peripheral arterial emboli. American Journal of Surgery. 1984;**148**:14-19. DOI: 10.1016/0002-9610(84)90283-6

[20] Harry L, Morrison I. Catheter-directed thrombolysis for acute limb ischemia. Seminars in Interventional Radiology. 2006;**23**:258-269. DOI: 10.1055/s-2006-948765

[21] Colman RW, Hirsh J, Marder VJ, et al. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Philadelphia: Lippincott Williams & Wilkins; 2006. 1827 p

[22] Hinton RC, Kistler JP, Fallon JT, Friedlich AL, Fisher CM. Influence of etiology of atrial fibrillation on incidence of systemic embolism. The American Journal of Cardiology. 1977;**40**:509-513. DOI: 10.1016/0002-9149(77)90064-9

[23] Haimovici H. Peripheral arterial embolism: A study of 330 unselected cases of embolism of the extremities. Angiology. 1950;**1**:20-45. DOI: 10.1177/000331975000100103

[24] Abbott WM, Maloney RD, McCabe CC, Lee CE, Wirthlin LS. Arterial embolism: A 44 year perspective. American Journal of Surgery. 1982;**143**:460-464. DOI: 10.1016/0002-9610(82)90196-9

[25] Tawes RL Jr, Harris EJ, Brown WH, Shoor PM, Zimmerman JJ, Sydorak GR, et al. Arterial thromboembolism. A 20-year perspective. Archives of Surgery. 1985;**120**:595-599. DOI: 10.1001/archsurg.1985.01390290073012

[26] Lyaker MR, Tulman DB, Dimitrova GT, Pin RH, Papadimos TJ. Arterial embolism. International journal of critical illness and injury science. 2013;**3**:77-87. DOI: 10.4103/2229-5151.109429

[27] Kitts D, Bongard FS, Klein SR. Septic embolism complicating infective endocarditis. Journal of Vascular Surgery. 1991;**14**: 480-485 ; discussion 485-487. DOI: 10.1016/0741-5214(91)90241-L

[28] Kalliafas S, Albertini JN, Macierewicz J, Yusuf SW, Whitaker SC, Davidson I, et al. Stent-graft migration after endovascular repair of abdominal aortic aneurysm. Journal of Endovascular Therapy. 2002;**9**:743-747. DOI: 10.1177/152660280200900605

[29] Bui JT, West DL, Pinto C, Gramling-Babb P, Owens CA. Right ventricular migration and endovascular removal of an inferior vena cava filter. Journal of Vascular and Interventional Radiology. 2008;**19**: 141-144. DOI: 10.1016/j.jvir.2007.09.014

[30] Tourmousoglou C, Karkos C, Fidanis T, Theofilogiannakos EK, Hytiroglou P, Pitsis A. An unusual case of arterial embolism in an adolescent with a mitral valve repair with a ring. The Annals of Thoracic Surgery. 2017;**104**:e315-e317. DOI: 10.1016/j.athoracsur.2017.04.051

[31] Ward R, Jones D, Haponik EF. Paradoxical embolism. An underrecognized problem. Chest. 1995;**108**:549-558. DOI: 10.1378/chest.108.2.549

[32] Saric M, Kronzon I. Cholesterol embolization syndrome. Current Opinion in Cardiology. 2011;**26**:472-479. DOI: 10.1097/HCO.0b013e32834b7fdd

[33] Cross SS. How common is cholesterol embolism? Journal of Clinical Pathology. 1991;**44**:859-861. DOI: 10.1136/jcp.44.10.859

[34] Mayo RR, Swartz RD. Redefining the incidence of clinically detectable atheroembolism. The American Journal of Medicine. 1996;**100**:524-529. DOI: 10.1016/S0002-9343(95)00059-3

[35] Moolenaar W, Lamers CB. Cholesterol crystal embolization in the Netherlands. Archives of Internal Medicine. 1996;**156**:653-657. DOI: 10.1001/archinte.1996.00440060081009

[36] Scolari F, Tardanico R, Zani R, Pola A, Viola BF, Movilli E, et al. Cholesterol crystal embolism: A recognizable cause of renal disease. American Journal of Kidney Diseases. 2000;**36**:1089-1109. DOI: 10.1053/ajkd.2000.19809

[37] Higginson A, Alaeddin F, Fishwick G, Bolia A. "Push and park": An alternative strategy for management of embolic complication during balloon angioplasty. European Journal of Vascular and Endovascular Surgery. 2001;**21**:279-282. DOI: 10.1053/ejvs.2001.1324

[38] Karnabatidis D, Katsanos K, Kagadis GC, Ravazoula P, Diamantopoulos A, Nikiforidis GC, et al. Distal embolism during percutaneous revascularization of infra-aortic arterial occlusive disease: An underestimated phenomenon. Journal of Endovascular Therapy. 2006;**13**:269-280. DOI: 10.1583/05-1771.1

[39] Perry MO. Compartment syndromes and reperfusion injury. The Surgical Clinics of North America. 1988;**68**:853-864. DOI: 1016/S0039-6109(16)44590-1

[40] Blebea J, Kerr JC, Franco CD, Padberg FT Jr, Hobson RW 2nd. Technetium 99m pyrophosphate quantitation of skeletal muscle ischemia and reperfusion injury. Journal of Vascular Surgery. 1988;**8**:117-124. DOI: 10.1016/0741-5214(88)90397-7

[41] Silvers LW, Royster TS, Mulcare RJ. Peripheral arterial emboli and factors in their recurrence rate. Annals of Surgery. 1980;**192**:232-236

[42] Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: Revised version. Journal of Vascular Surgery. 1997;**26**:517-538. DOI: 10.1016/S0741-5214(97)70045-4

[43] Busuttil RW, Keehn G, Milliken J, Paredero VM, Baker JD, Machleder HI, et al. Aortic saddle embolus. A twenty-year experience. Annals of Surgery. 1983;**197**:698-706

[44] Hartung MP, Grist TM, Francois CJ. Magnetic resonance angiography: Current status and future directions. Journal of Cardiovascular Magnetic Resonance. 2011;**13**:19. DOI: 10.1186/1532-429X-13-19

[45] Egeblad H, Andersen K, Hartiala J, Lindgren A, Marttila R, Petersen P, et al. Role of echocardiography in systemic arterial embolism. A review with recommendations. Scandinavian Cardiovascular Journal. 1998;**32**:323-342. DOI: 10.1080/14017439850139780

[46] Gossage JA, Ali T, Chambers J, Burnand KG. Peripheral arterial embolism: Prevalence, outcome, and the role of echocardiography in management. Vascular and Endovascular Surgery. 2006;**40**:280-286. DOI: 10.1177/1538574406291820

[47] Kvilekval KH, Yunis JP, Mason RA, Giron F. After the blue toe: Prognosis of noncardiac arterial embolization in the lower extremities. Journal of Vascular Surgery. 1993;**17**:328-334; discussion 334-325. DOI: 10.1016/0741-5214(93)90418-L

[48] Nevins MA, Saran M, Bright M, Lyon LJ. Pitfalls in interpreting serum creatine phosphokinase activity. Journal of the American Medical Association. 1973;**224**:1382-1387. DOI: 10.1001/jama.1973.03220240032008

[49] Russell SM, Bleiweiss S, Brownlow K, Elevitch FR. Ischemic rhabdomyolysis and creatine phosphokinase isoenzymes: A diagnostic pitfall. Journal of the American Medical Association. 1976;**235**:632-633. DOI: 10.1001/jama.1976.03260320040023

[50] Eliason JL, Wainess RM, Proctor MC, Dimick JB, Cowan JA Jr, Upchurch GR Jr, et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. Annals of Surgery. 2003;**238**:382-389; discussion 389-390. DOI: 10.1097/01.sla.0000086663.49670.d1

[51] Lurie F, Vaidya V, Comerota AJ. Clinical outcomes and cost-effectiveness of initial treatment strategies for nonembolic acute limb ischemia in real-life clinical settings. Journal of Vascular Surgery. 2015;**61**:138-146. DOI: 10.1016/j.jvs.2014.07.086

[52] Baril DT, Patel VI, Judelson DR, Goodney PP, McPhee JT, Hevelone ND, et al. Outcomes of lower extremity bypass performed for acute limb ischemia. Journal of Vascular Surgery. 2013;**58**:949-956. DOI: 10.1016/j.jvs.2013.04.036

[53] Berridge DC, Hopkinson BR, Makin GS. Acute lower limb arterial ischaemia: A role for continuous oxygen inhalation. The British Journal of Surgery. 1989;**76**:1021-1023. DOI: 10.1002/bjs.1800761011

[54] Linnemann B, Schindewolf M, Zgouras D, Erbe M, Jarosch-Preusche M, Lindhoff-Last E. Are patients with thrombophilia and previous venous thromboembolism at higher risk to arterial thrombosis? Thrombosis Research. 2008;**121**:743-750. DOI: 10.1016/j.thromres.2007.07.014

[55] Lijfering WM, Coppens M, van de Poel MH, Middeldorp S, Hamulyak K, Bank I, et al. The risk of venous and arterial thrombosis in hyperhomocysteinaemia is low and mainly depends on concomitant thrombophilic defects. Thrombosis and Haemostasis. 2007;**98**:457-463. DOI: 10.1160/TH07-02-0138

[56] Deitcher SR, Carman TL, Sheikh MA, Gomes M. Hypercoagulable syndromes: Evaluation and management strategies for acute limb ischemia. Seminars in Vascular Surgery. 2001;**14**:74-85. DOI: 10.1053/svas.2001.23156

[57] de Moerloose P, Boehlen F. Inherited thrombophilia in arterial disease: A selective review. Seminars in Hematology. 2007;**44**:106-113. DOI: 10.1053/j.seminhematol.2007.01.008

[58] Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004;**126**:401S-428S. DOI: 10.1378/chest.126.3_suppl.401S

[59] Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest. 2008;**133**:110S-112S. DOI: 10.1378/chest.08-0652

[60] Murray GDW. Heparin in thrombosis and embolism. The British Journal of Surgery. 1940;**27**:567-598. DOI: 10.1002/bjs.18002710718

[61] Blaisdell FW, Steele M, Allen RE. Management of acute lower

extremity arterial ischemia due to embolism and thrombosis. Surgery. 1978;**84**:822-834

[62] Ram B, George R. Nontraumatic acute limb ischemia–presentation, evaluation, and management. Indian Journal of Vascular and Endovascular Surgery. 2017;**4**:192

[63] Fogarty TJ, Cranley JJ, Krause RJ, Strasser ES, Hafner CD. A method for extraction of arterial emboli and thrombi. Surgery, Gynecology & Obstetrics. 1963;**116**:241-244

[64] de Donato G, Setacci F, Sirignano P, Galzerano G, Massaroni R, Setacci C. The combination of surgical embolectomy and endovascular techniques may improve outcomes of patients with acute lower limb ischemia. Journal of Vascular Surgery. 2014;**59**: 729-736. DOI: 10.1016/j.jvs.2013.09.016

[65] Levin BH, Giordano JM. Delayed arterial embolectomy. Surgery, Gynecology & Obstetrics. 1982;**155**:549-551

[66] van den Berg JC. Thrombolysis for acute arterial occlusion. Journal of Vascular Surgery. 2010;**52**:512-515. DOI: 10.1016/j.jvs.2010.01.080

[67] Earnshaw JJ. Thrombolytic therapy in the management of acute limb ischaemia. The British Journal of Surgery. 1991;**78**:261-269. DOI: 10.1002/bjs.1800780304

[68] Hess H. Thrombolytic therapy in peripheral vascular disease. The British Journal of Surgery. 1990;**77**:1083-1084. DOI: 10.1002/bjs.1800771003

[69] Lawrence PF, Goodman GR. Thrombolytic therapy. The Surgical Clinics of North America. 1992;**72**:899-918

[70] Hanover TM, Kalbaugh CA, Gray BH, Langan EM 3rd, Taylor SM, Androes MP, et al. Safety and efficacy of reteplase for the treatment of acute arterial occlusion: Complexity of underlying lesion predicts outcome. Annals of Vascular Surgery. 2005;**19**:817-822. DOI: 10.1007/s10016-005-8047-2

[71] Rush DS, Gewertz BL, Lu CT, Neely SM, Ball DG, Beasley M, et al. Selective infusion of streptokinase for arterial thrombosis. Surgery. 1983;**93**:828-833

[72] Dardik H, Sussman BC, Kahn M, Greweldinger J, Adler J, Mendes D, et al. Lysis of arterial clot by intravenous or intra-arterial administration of streptokinase. Surgery, Gynecology & Obstetrics. 1984;**158**:137-140

[73] Berni GA, Bandyk DF, Zierler RE, Thiele BL, Strandness DE Jr. Streptokinase treatment of acute arterial occlusion. Annals of Surgery. 1983;**198**:185-191

[74] Slany J, Enzenhofer V, Karnik R. Local thrombolysis in arterial occlusive disease. Angiology. 1984;**35**:231-237. DOI: 10.1177/000331978403500405

[75] Ouriel K, Shortell CK, Green RM, DeWeese JA. Differential mechanisms of failure of autogenous and non-autogenous bypass conduits: An assessment following successful graft thrombolysis. Cardiovascular Surgery. 1995;**3**:469-473. DOI: 10.1177/096721099500300505

[76] Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or peripheral arterial surgery (TOPAS) investigators. The New England Journal of Medicine. 1998;**338**:1105-1111. DOI: 10.1056/NEJM199804163381603

[77] Comerota AJ, Weaver FA, Hosking JD, Froehlich J, Folander H, Sussman B,

et al. Results of a prospective, randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts. American Journal of Surgery. 1996;**172**: 105-112. DOI: 10.1016/S0002-9610(96)00129-8

[78] Working Party on Thrombolysis in the Management of Limb I. Thrombolysis in the management of lower limb peripheral arterial occlusion–a consensus document. Journal of Vascular and Interventional Radiology. 2003;**14**:S337-S349. DOI: 10.1016/S1051-0443(07)61244-5

[79] Yusuf SW, Whitaker SC, Gregson RH, Wenham PW, Hopkinson BR, Makin GS. Prospective randomised comparative study of pulse spray and conventional local thrombolysis. European Journal of Vascular and Endovascular Surgery. 1995;**10**:136-141. DOI: 10.1016/S1078-5884(05)80104-2

[80] Huettl EA, Soulen MC. Thrombolysis of lower extremity embolic occlusions: A study of the results of the STAR registry. Radiology. 1995;**197**:141-145. DOI: 10.1148/radiology.197.1.7568812

[81] Schleder S, Diekmann M, Manke C, Heiss P. Percutaneous aspiration thrombectomy for the treatment of arterial thromboembolic occlusions following percutaneous transluminal angioplasty. Cardiovascular and Interventional Radiology. 2015;**38**: 60-64. DOI: 10.1007/s00270-014-0857-6

[82] Horsch AD, van Oostayen J, Zeebregts CJ, Reijnen MM. The Rotarex(R) and Aspirex(R) mechanical thrombectomy devices. Surgical Technology International. 2009;**18**:185-192

[83] Starck EE, McDermott JC, Crummy AB, Turnipseed WD, Acher CW, Burgess JH. Percutaneous aspiration thromboembolectomy. Radiology. 1985;**156**:61-66. DOI: 10.1148/radiology.156.1.3159042

[84] Reekers JA, Kromhout JG, Spithoven HG, Jacobs MJ, Mali WM, Schultz-Kool LJ. Arterial thrombosis below the inguinal ligament: Percutaneous treatment with a thrombosuction catheter. Radiology. 1996;**198**:49-53. DOI: 10.1148/radiology.198.1.8539405

[85] Rilinger N, Gorich J, Scharrer-Pamler R, Vogel J, Tomczak R, Kramer S, et al. Short-term results with use of the Amplatz thrombectomy device in the treatment of acute lower limb occlusions. Journal of Vascular and Interventional Radiology. 1997;**8**:343-348. DOI: 10.1016/S1051-0443(97)70569-4

[86] Wagner HJ, Starck EE. Acute embolic occlusions of the infrainguinal arteries: Percutaneous aspiration embolectomy in 102 patients. Radiology. 1992;**182**:403-407. DOI: 10.1148/radiology.182.2.1732957

[87] Aune S, Trippestad A. Operative mortality and long-term survival of patients operated on for acute lower limb ischaemia. European Journal of Vascular and Endovascular Surgery. 1998;**15**:143-146. DOI: 10.1016/S1078-5884(98)80135-4

[88] Kuukasjarvi P, Salenius JP. Perioperative outcome of acute lower limb ischaemia on the basis of the national vascular registry. The Finnvasc study group. European Journal of Vascular Surgery. 1994;**8**:578-583. DOI: 10.1016/S0950-821X(05)80594-8

[89] Neuzil DF, Edwards WH Jr, Mulherin JL, Martin RS 3rd, Bonau R, Eskind SJ, et al. Limb ischemia: Surgical therapy in acute arterial occlusion. The American Surgeon. 1997;**63**:270-274

[90] Braithwaite BD, Davies B, Birch PA, Heather BP, Earnshaw JJ. Management of acute leg ischaemia

in the elderly. The British Journal of Surgery. 1998;**85**:217-220. DOI: 10.1046/j.1365-2168.1998.00577.x

[91] Dregelid EB, Stangeland LB, Eide GE, Trippestad A. Patient survival and limb prognosis after arterial embolectomy. European Journal of Vascular Surgery. 1987;**1**:263-271. DOI: 10.1016/S0950-821X(87)80078-6

[92] Baxter-Smith D, Ashton F, Slaney G. Peripheral arterial embolism. A 20 year review. The Journal of Cardiovascular Surgery. 1988;**29**:453-457

[93] Sexton WL, Korthuis RJ, Laughlin MH. Ischemia-reperfusion injury in isolated rat hindquarters. Journal of Applied Physiology (Bethesda, MD: 1985). 1990;**68**:387-392. DOI: 10.1152/jappl.1990.68.1.387

[94] Papalambros EL, Panayiotopoulos YP, Bastounis E, Zavos G, Balas P. Prophylactic fasciotomy of the legs following acute arterial occlusion procedures. International Angiology. 1989;**8**:120-124

[95] Mubarak SJ, Owen CA, Hargens AR, Garetto LP, Akeson WH. Acute compartment syndromes: Diagnosis and treatment with the aid of the wick catheter. The Journal of Bone and Joint Surgery. American Volume. 1978;**60**:1091-1095

[96] Rollins DL, Bernhard VM, Towne JB. Fasciotomy: An appraisal of controversial issues. Archives of Surgery. 1981;**116**:1474-1481. DOI: 10.1001/archsurg.1981.01380230088014

[97] Haimovici H. Arterial embolism with acute massive ischemic myopathy and myoglobinuria: Evaluation of a hitherto unreported syndrome with report of two cases. Surgery. 1960;**47**:739-747

[98] Haimovici H. Proceedings: Myopathic-nephrotic-metabolic syndrome associated with massive acute arterial occlusions. The Journal of Cardiovascular Surgery. 1973;**14**:589-600

[99] Eliason JL, Wakefield TW. Metabolic consequences of acute limb ischemia and their clinical implications. Seminars in Vascular Surgery. 2009;**22**:29-33. DOI: 10.1053/j.semvascsurg.2009.01.001

[100] Braunwald E, Kloner RA. Myocardial reperfusion: A double-edged sword? The Journal of Clinical Investigation. 1985;**76**:1713-1719. DOI: 10.1172/JCI112160

[101] Bulkley GB. Pathophysiology of free radical-mediated reperfusion injury. Journal of Vascular Surgery. 1987;**5**:512-517. DOI: 10.1016/0741-5214(87)90085-1

[102] Perry MO. Postischemic cell membrane dysfunction. Journal of Vascular Surgery. 1990;**11**:179-180. DOI: 10.1016/0741-5214(90)90343-9

[103] Walker PM. Pathophysiology of acute arterial occlusion. Canadian Journal of Surgery. 1986;**29**:340-342

[104] Bradbury AW, Brittenden J, McBride K, Ruckley CV. Mesenteric ischaemia: A multidisciplinary approach. The British Journal of Surgery. 1995;**82**:1446-1459. DOI: 10.1002/bjs.1800821105

[105] Brezis M, Rosen S. Hypoxia of the renal medulla—Its implications for disease. The New England Journal of Medicine. 1995;**332**:647-655. DOI: 10.1056/NEJM199503093321006

[106] Cagin YF, Atayan Y, Sahin N, Parlakpinar H, Polat A, Vardi N, et al. Beneficial effects of dexpanthenol on mesenteric ischemia and reperfusion injury in experimental rat model. Free Radical Research. 2016;**50**:354-365. DOI: 10.3109/10715762.2015.1126834

[107] Cannistra M, Ruggiero M, Zullo A, Gallelli G, Serafini S, Maria M, et al. Hepatic ischemia reperfusion injury: A systematic review of literature and the role of current drugs and biomarkers. International Journal of Surgery. 2016;**33**(Suppl 1):S57-S70. DOI: 10.1016/j.ijsu.2016.05.050

[108] Chen J, Vemuri C, Palekar RU, Gaut JP, Goette M, Hu L, et al. Antithrombin nanoparticles improve kidney reperfusion and protect kidney function after ischemia-reperfusion injury. American Journal of Physiology. Renal Physiology. 2015;**308**:F765-F773. DOI: 10.1152/ajprenal.00457.2014

[109] Collard CD, Vakeva A, Morrissey MA, Agah A, Rollins SA, Reenstra WR, et al. Complement activation after oxidative stress: Role of the lectin complement pathway. The American Journal of Pathology. 2000;**156**:1549-1556. DOI: 10.1016/S0002-9440(10)65026-2

[110] Haljamae H, Enger E. Human skeletal muscle energy metabolism during and after complete tourniquet ischemia. Annals of Surgery. 1975;**182**:9-14

[111] Hayes PG, Liauw S, Smith A, Romaschin AD, Walker PM. Exogenous magnesium chloride-adenosine triphosphate administration during reperfusion reduces the extent of necrosis in previously ischemic skeletal muscle. Journal of Vascular Surgery. 1990;**11**:441-447. DOI: 10.1016/0741-5214(90)90245-6

[112] Del Maestro RF. An approach to free radicals in medicine and biology. Acta Physiologica Scandinavica. Supplementum. 1980;**492**:153-168

[113] Huk I, Nanobashvili J, Neumayer C, Punz A, Mueller M, Afkhampour K, et al. L-arginine treatment alters the kinetics of nitric oxide and superoxide release and reduces ischemia/reperfusion injury in skeletal muscle. Circulation. 1997;**96**:667-675

[114] Wajant H, Pfizenmaier K, Scheurich P. Tumor necrosis factor signaling. Cell Death and Differentiation. 2003;**10**:45-65. DOI: 10.1038/sj.cdd.4401189

[115] Anner H, Kaufman RP Jr, Valeri CR, Shepro D, Hechtman HB. Reperfusion of ischemic lower limbs increases pulmonary microvascular permeability. The Journal of Trauma. 1988;**28**:607-610

[116] Back M. Leukotriene signaling in atherosclerosis and ischemia. Cardiovascular Drugs and Therapy. 2009;**23**:41-48. DOI: 10.1007/s10557-008-6140-9

[117] Karam H, Bruneval P, Clozel JP, Loffler BM, Bariety J, Clozel M. Role of endothelin in acute renal failure due to rhabdomyolysis in rats. The Journal of Pharmacology and Experimental Therapeutics. 1995;**274**:481-486

[118] Zager RA, Burkhart KM, Conrad DS, Gmur DJ. Iron, heme oxygenase, and glutathione: Effects on myohemoglobinuric proximal tubular injury. Kidney International. 1995;**48**:1624-1634. DOI: 10.1038/ki.1995.457

[119] Beyersdorf F, Schlensak C. Controlled reperfusion after acute and persistent limb ischemia. Seminars in Vascular Surgery. 2009;**22**:52-57. DOI: 10.1053/j.semvascsurg.2009.01.005

[120] Ricci MA, Graham AM, Corbisiero R, Baffour R, Mohamed F, Symes JF. Are free radical scavengers beneficial in the treatment of compartment syndrome after acute arterial ischemia? Journal of Vascular Surgery. 1989;**9**:244-250. DOI: 10.1016/0741-5214(89)90043-8

[121] Ozcan AV, Sacar M, Aybek H, Bir F, Demir S, Onem G, et al. The effects

of iloprost and vitamin C on kidney as a remote organ after ischemia/reperfusion of lower extremities. The Journal of Surgical Research. 2007;**140**:20-26. DOI: 10.1016/j.jss.2006.04.031

[122] Celoria G, Zarfos K, Berman J. Effects of acute lower limb ischemia on femoral venous efflux. Angiology. 1990;**41**:439-444. DOI: 10.1177/000331979004100604

[123] Perry MO, Fantini G. Ischemia: Profile of an enemy. Reperfusion injury of skeletal muscle. Journal of Vascular Surgery. 1987;**6**:231-234. DOI: 10.1016/0741-5214(87)90033-4

IntechOpen