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ACUTE LIMB ISCHEMIA: AN 2017 UPDATE

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Summary:

Acute Limb ischemia (ALI) is one of the most treatable and potentially devastating presentations of PAD. It represents one of the toughest challenges encountered by vascular specialists. The diagnosis and initial assessment are largely clinical, and diagnostic errors can cost dear to the patient. Amputation and death rates remain high despite intervention, which is in contrast to major advances in the treatment of many other vascular diseases. Acute ischemia is often an end-of-life condition presented by a patient with multiple medical co-morbidities. This review focuses on the most recent literature in the field of epidemiology, clinical presentation and assessment, treatment and prognosis.
Key words: acute limb ischemia, Anticoagulation, limb salvage, endovascular procedures, vascular surgery.

Introduction

According to the 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease[1], and to the TASC II Working Group: Inter-Society Consensus for the Management of Peripheral Arterial Disease[2], Acute Limb ischemia (ALI) is any sudden, recent decrease or worsening in limb perfusion less than 14 days causing a potential threat to limb viability.

It represents one of the toughest challenges encountered by vascular specialists. The diagnosis and initial assessment are largely clinical, and diagnostic errors can cost dear to the patient. Amputation and death rates remain high despite intervention, which is in contrast to major advances in the treatment of many other vascular diseases. Acute ischemia is often an end-of-life condition presented in a patient with multiple medical comorbidities. Therefore a careful clinical assessment of the individual is as important as assessment of the limb. Unlike many other vascular con¬ditions, there is not one definitive treatment; a variety of modalities are available, including anticoagulation, operative intervention, thrombolysis, and mechanical thrombectomy. Selection of the most appropriate intervention or combination of interventions can be critical to the eventual outcome [3].

GENERAL CONSIDERATIONS

Epidemiology

Very few published epidemiological data are available to establish the real incidence of ALI in the general population and this incidence varies according to the authors. In the whole population the acute ischemia of limbs and organs happens in 14 cases per 100,000 inhabitants from 10 to 16% in the angiosurgery [4-6]. The incidence of ALI is 9–16 cases per 100,000 persons per year for the lower extremity [7-9]. In the USA, the incidence of hospitalization for ALI decreased from 45.7 per 100,000 to 26.0 per 100,000 [10]. In England, Overall hospital admissions for ALI rose from 60.3 in 1999 to 94.3 in 2011 per 100,000 of the population in those aged ≥60 years. There was a suggestion of a hinge point in 2003 with an average annual rise of 6.2% thereafter [11]

Etiology and Pathogenesis Etiology

Excluding trauma and iatrogenic causes, there are two main reasons to the occurrence of acute limb ischemia: arterial embolism and thrombosis [3]. Factors that cause ALI are numerous and are listed in Table I Distinction between thrombosis and embolism is important in terms of diagnosis and prognosis, but it may not be crucial when deciding on the form of treatment [3]. Nowadays, the major cause of ALI (approximately 85 % of cases) is arterial thrombosis, primarily caused by underlying atherosclerosis. The remaining 10 – 15 % of patients suffers from peripheral embolism (mostly of cardiac origin) [12]

Table 1 : The causes of acute limb ischemia **[6, 13]**

Embolus
Atrial fibrillation
Valvular heart disease
Endocarditis
Myocardial infarction (with mural thrombus)
Aortic and peripheral arterial aneurysms
Ulcerated atherosclerotic plaque with intraplaque hemorrhage
Paradoxical embolus
Atrial myxoma
Cardiomyopathy
Thrombosis
Atherosclerotic occlusive disease
Aortic and peripheral arterial aneurysms
Intraplaque hemorrhage with arterial sthenosis and occlusion
Hypercoagulable states (C ar S protein deficiencies)
Entrapment syndromes
Stasis/low-flow states
Drugs of abuse
Trauma
Penetrating
Blunt
Interventional vascular procedures

Pathogenesis[3]

Embolism

Embolism from the Greek embolos, or “plug” is the result of material passing through the arterial tree and obstructing a peripheral artery. Usually the source of the embolus is the heart, and the material is mural thrombus that has accumulated and detached. The other main cause is atherosclerotic debris from a diseased proximal artery, often the thoracic aorta, in individuals with a heavy burden of atherosclerotic disease. Paradoxical embolism occurs when a clot from the venous system, usually a deep venous thrombosis, travels through a patent foramen ovale into the arterial system. The clinical clue is acute arterial ischemia in a young patient with known deep venous thrombosis. Once the embolus detaches, it passes easily through large arteries and lodges peripherally, usually at an arterial bifurcation, where vessels naturally narrow. Emboli can occlude any artery, but in the legs, the common femoral and popliteal arteries are commonly obstructed. Only large emboli, so-called saddle emboli, occlude the normal aortic bifurcation. In the upper extremity, the brachial artery bifurcation and the brachial artery at the takeoff of the profunda brachialis artery are frequent locations for emboli to stop. Embolic ischemia is usually catastrophic because it often occurs in rather normal arteries, without any established collaterals.

Thrombosis

Thrombosis results from blood clotting within an artery, which can be caused by progressive atherosclerotic obstruction, hypercoagulability, or aortic or arterial dissection. Thrombotic occlusion is most commonly the result of progressive atherosclerotic narrowing in peripheral arteries of the leg. Once a stenosis becomes critical, platelet thrombus develops on the stenotic lesion, leading to an acute arterial occlusion. Another significant cause of acute limb ischemia is the occlusion of an existing patent bypass graft. In situ thrombus formation is usually secondary to underlying disease such as atherosclerosis [14].

Pathophysiology [15]

Irrespective of the underlying etiology, arterial occlusion causes diminished perfusion of the limb [14]. Acute ischemia is the result of a sudden drop in the arterial supply to the limb [3]. It leads to severe lesions, or even irreversible, aggravated during the reperfusion. Data in the literature agree to say that the most vulnerable tissue in ischemia is the nervous tissue, more precisely the neuromuscular junction [16]. Muscle damage becomes significant after six hours of ischemia [17]. The main determinants of severity Ischemic lesions are the pre-existing collateral arteries, duration of ischemia and temperature of limb [18]. Reperfusion injury causes local and systems disorders.

Ischemia

Ischemia leads to a deprivation of the input of substrates exogenous substances such as oxygen and free fatty acids and accumulation of metabolites such as H + ions and lactic products produced by the pathways of anaerobic metabolism. We observed an initial decrease in glycogen and creatine phosphate followed by a secondary decrease in concomitant ATP of the onset of necrosis tissue occurring towards the 4th-6th hour [19].

Reperfusion

It is during reperfusion that the majority of complications appear. During reperfusion, a release of muscle degradation substances (muscle enzymes (aspartate aminotrans-ferase (AST), Lactate dehydrogenase (LDH) creatine phosphokinase (CPK)), myoglobin, lactates, potassium, H + ions) can lead to severe metabolic acidosis and lead to multiviscal failures with the onset of insufficiency renal failure, respiratory distress, or even cardiac arrest. Hyper-kalemia observed after ischemia-reperfusion originates from cell lysis which causes an increase of potassium in the extracellular medium, followed by release in the circulation: it is the wash-out phenomenon.

Clinical Presentation

The symptoms displayed by vascular occlusion depend on the size of the artery occluded and whether collaterals have developed beforehand.

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 entirely asymptomatic [3].

Symptoms [20]

Embolic occlusions are usually very sudden and of great intensity, such a way that patients often present within a few hours of onset. Acute arterial occlusion is associated with intense spasm in the distal arterial tree, and initially, the limb will appear “marble” white. Over the next few hours, the spasm relaxes and the skin fills with deoxygenated blood leading to mottling that is light blue or purple, has a fine reticular pattern, and blanches on pressure.2 [21]. At this stage, the limb is still salvageable. The classical description of patients with ALI is represented by the “six Ps”: pain, pallor, paralysis, pulse deficit, paresthesia, and poikilothermia [22]. Pallor and the level of coldness (poikilothermia) are important to record to evaluate the progression of ischemia. The pulse deficit is helpful determining the site of occlusion. It should also be remembered that sensory capabilities, such as light touch, two-point tactile discrimination, proprioception, and vibratory perception, are lost early on. Finally, profound paralysis with complete lack of sensation indicates an irreversible state of ischemia, and the patient may be best treated with primary amputation [5] Clinical Assessment

The initial assessment of acute critical ischemia involves an evaluation of both the limb and the patient as a whole.

History

History should be considered in an attempt to define the cause of ischemia. Historically, patients with emboli had valvular heart disease but no evidence of peripheral vascular disease or other atherosclerotic conditions; however, the presence of atherosclerosis no longer rules out embolism. Patients with acute-on-chronic thrombosis often give a history of prior intermittent claudication in the ipsilateral or contralateral leg. A full medical history is important because it may reveal other associated diseases such as diabetes mellitus.

Risk factors for atherosclerotic disease should be sought, including smoking, hypertension, hyperlipidemia, and family history [3].

Risk factors

It is often difficult to distinguish an embolus from a thrombosis, but embolic occlusions should be suspected in patients with the following features: (1) acute onset, where the patient is often able to accurately time the moment of the event; (2) a history of embolism; (3) a known embolic source, such as cardiac arrhythmias; (4) no prior history of intermittent claudication; and (5) normal pulse and Doppler examination in the unaffected limb.1 [2] Differential diagnoses of ALI are represented in Table II.

Physical Findings

Examination of the leg is used to define the severity of the ischemia and is therefore fundamental. The well-known rule of pain, pallor, paresis, pulse deficit, paresthesia, and poikilothermia remains a good guide to both symptoms and signs. A full vascular examination reveals the level of the occlusion by the loss of arterial pulsation. A strong pulse can, however, mask an occlusion at that level because of the water-hammer effect. Other possible sources of embolization may become apparent, such as aortic or popliteal aneurysm or cardiac abnormalities such as atrial fibrillation. Patients with acute leg ischemia are often older adults with multiple comorbidities, and a full physical examination should be undertaken because the final outcome may depend as much on associated conditions as on the severity of the leg ischemia. Hand-held Doppler examination is also a basic part of the examination. Pedal arterial signals may be absent or reduced. The presence of normal biphasic signals excludes the diagnosis. Soft monophasic signals are associated with patent distal vessels but proximal arterial occlusion. In total, according to the 2016 AHA/ACC Guideline on the Management of Patients, with Lower Extremity Peripheral Artery Disease [1], ALI is a medical emergency and must be recognized rapidly.

The time constraint is due to the period that skeletal muscle will tolerate ischemia—roughly 4 to 6 hours [23]. A rapid assessment of limb viability and ability to restore arterial blood flow should be performed by a clinician able to either complete the revascularization or triage the patient [24]. Lower extremity symptoms in ALI can include both pain and loss of function. The longer these symptoms are present, the less likely the possibility of limb salvage [25, 26]. Clinical assessment must include symptom duration, pain intensity, and motor and sensory deficit severity to distinguish a threatened from a nonviable extremity. Hand-held Doppler examination is also a basic part of the examination. Pedal arterial signals may be absent or reduced. The presence of normal biphasic signals excludes the diagnosis. 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. The arteries may be patent but with little flow, or they may be occluded with thrombus. In severe ischemia, ankle Doppler pressures

Table II: Rutherford classification of acute limb ischemia [32]

Class	Category	Prognosis	Sensory loss	Muscle weakness	Arterial Doppler	Venous Doppler
I	Viable	No immediate limb threat	None	None	Audible	Audible
IIA	Threatened: marginal	Salvageable if treated promptly	Minimal-none	None	+/-Audible	Audible
IIB	Threatened: Immediate	Salvageable if treated immediately	More than just toes	Mild-moderate	Rare audible	Audible
III	Irreversible	Limb loss or permanent damage	Profound	Profound	None	None

are impossible to measure, partly owing to the lack of signal but also because of muscle tenderness. In less severe ischemia, an ankle pressure of 30 to 50mmHg can be expected, and an ankle-brachial index of about 0.3 is diagnostic of subcritical acute ischemia. Doppler can also be used to examine the extremity veins. In particular, the lack of a venous signal in the popliteal fossa suggests popliteal venous occlusion, which is a particularly poor prognostic sign in a patient with acute arterial ischemia.

Classification of Acute Limb Ischemia

Acute limb ischemia used to be classified according to cause—thrombosis or embolism—because this had implications for treatment and prognosis. Patients with thrombosis tended to be younger but had a higher risk of major amputation. Patients with emboli tended to be older and had a higher risk of dying after treatment [27, 28]. It has become clear that this is not a useful classification because there is no way of proving definitively whether an occlusion is thrombus or embolus. A more valuable method of classification is based on the severity of the arterial ischemia, which is helpful in determining the urgency of intervention and its implications for outcome [29, 30].

The Society for Vascular Surgery and the International Society for Cardiovascular Surgery have published definitions of acute leg ischemia that are valuable for treatment and prognosis (Table II) [31, 32]. These standards were modified in 2007 by a larger group—the Trans-Atlantic Inter-Society Consensus—which defined acute ischemia as any sudden decrease in limb perfusion causing a potential threat to limb viability [2].

Diagnosis

Following clinical assessments and classification, the anatomic location of the arterial occlusion can be diagnosed with a high degree of reliability. The anatomic location can be: aortic, iliac, femoro-popliteal, popliteal and infra-popliteal. In view of the symptoms presented by the patient, it is necessary to eliminate other differential diagnoses of ALI represented in Table 3.

Table III: Differential diagnosis of A[2].

Conditions mimicking ALI
• Systemic shock (especially if associated with chronic occlusive disease)
• Phlegmasia cerulea dolens
• Acute compressive neuropathy
Differential diagnosis of ALI (other than acute PAD)
• Trauma
• Dissection
• Arteritis
• Hypercoagulable states
• Popliteal adventitial cyst
• Popliteal entrapment
• Compartment syndrome
Acute PAD
• Atherosclerotic stenosed artery thrombosis
• Arterial bypass graft thrombosis

Investigation

Investigation may be valuable in confirming the clinical diagnosis and planning the appropriate treatment for patients with acute ischemia. However, when the ischemia is critical, there may be no time for investigation if direct operative intervention is required. It is possible to employ on-table angiography to assist in decision making in the operating room. Depending on the time available, a number of methods can be used to definitively determine the site and nature of the arterial occlusion.

This investigation includes: Computed Tomography, Ultrasound, Transfemoral Arteriography, Magnetic Resonance Angiography, and Echocardiography

Treatment

Initial Management

Once the diagnosis of acute ischemia has been established and its severity classified, a number of immediate interventions are possible.

Anticoagulation and Supportive Measures

Systemic anticoagulation with unfrac-tionated heparin should be initiated to minimize the risk of further clot propagation and to prevent microvascular thrombosis of underperfused distal vessels. An initial weight-based bolus of 100 mg/kg is appropriate for most patients followed by an intravenous infusion of 1000 U/hr. If urgent operation is not undertaken, the heparin dose should be titrated to maintain an activated partial thromboplastin time between 60 and 100 seconds or 2.0 to 3.0 times normal values.

Other measures that may be beneficial in patients with ALI include intravenous hydration, supplemental oxygen, and intravenous analgesia.

Treatment options

Endovascular Treatment

Endovascular procedures offer less invasive revascularization strategies for sick or elderly patients with decreased morbidity and mortality. Currently available percutaneous endovascular procedures include catheter-directed thrombolysis, pharmaco-mechanical thrombolysis, catheter-directed thrombus aspiration, and percutaneous mechanical thrombectomy [8, 33]. These techniques clear the occluding thrombus from a peripheral artery with a minimally invasive approach, restore blood flow to the extremity, and allow the identification of underlying lesions responsible for the occlusive event. Culprit lesions may then be addressed in a directed mode with an endovascular procedure such as angioplasty, stenting, or atherectomy.

Peripheral thrombolytic therapy is administered through a catheter-directed approach to achieve regional thrombus dissolution with minimal systemic fibrinolysis. However, a moderate systemic proteolytic state often results from the use of thrombolytic agents, limiting their use to patients without contraindications to such a state (Table IV).

Table IV: Contraindications to Pharmacologic Thrombolytic Agents [34-36]

Absolute Contraindications

- Active bleeding disorder
- Gastrointestinal bleeding within 10 days
- Cerebrovascular event within 6 months
- Intracranial or spinal surgery within 3 months
- Head injury within 3 months

Relative Contraindications

- Major surgery or trauma within 10 days
- Hypertension (systolic >180 mm Hg or diastolic >110 mm Hg)
- Cardiopulmonary resuscitation within 10 days
- Puncture of noncompressible vessel
- Intracranial tumor
- Pregnancy
- Diabetic hemorrhagic retinopathy
- Recent eye surgery
- Hepatic failure
- Bacterial endocarditis

Open surgery: surgical revascularization

Balloon catheter thrombectomy, first introduced by Fogarty et al [37] in 1963, has been the cornerstone of therapy for the surgical management of ALI [38]. Techniques for salvage of an ischemic limb include: (1) balloon catheter thrombectomy or embolectomy, (2) bypass procedures to direct blood flow beyond the occlusion, (3) endarterectomy with or without patch angioplasty, and (4) hybrid procedures combining open and endovascular techniques.

Indications

Management strategy [39]

Heparin (generally intravenous unfractio-nated heparin) is given to all patients acutely [1, 2, 40]. This can stop thrombus propagation and may provide an anti-inflammatory effect that lessens the ischemia. Patients who have received heparin before the onset of ALI and have a decrease in platelet count may have heparin-induced thrombocytopenia [41, 42]. In this situation, a direct thrombin inhibitor is given, rather than heparin, if heparin-induced thrombocytopenia with thrombosis is suspected [1]. For marginally or immediately threatened limbs (Category IIa and IIb ALI [Figure 1]), revascular-iza-tion should be performed emergently (within 6 hours). For viable limbs (Category I ALI [Figure 1]), revascular-iza-tion should be performed on an urgent basis (within 6–24 hours).

Revascularization strategy

The revascularization strategy can range from catheter-directed thrombolysis to surgical thromboembolectomy. Available facilities and clinical expertise are factors that should be considered when determining the revascularization strategy. The technique that will provide the most rapid restoration of arterial flow with the least risk to the patient should be selected. For example, catheter-directed thrombolysis can provide rapid restoration of arterial flow to a viable or marginally threatened limb, particularly in the setting of recent occlusion, thrombosis of synthetic grafts, and stent thrombosis.367 If this is not available locally, surgical options for timely revascularization should be considered, along with the feasibility of timely transfer to a facility with the necessary expertise.

Amputation

For patients with Category III ALI, amputation should be performed as the index procedure. Prolonged duration of ischemia is the most common factor in patients requiring amputation for treatment of ALI. The risks associated with reconstruction outweigh the potential benefit in a limb that is already insensate or immobile because of prolonged ischemia. Patients who have an insensate and immobile limb in the setting of prolonged ischemia (>6 to unlikely to have potential for limb salvage. In addition, in this setting the reperfusion and circulation of ischemic metabolites can result in multiorgan failure and cardiovascular collapse. However, if pain can be controlled and there is no evidence of infection, amputation may be deferred if this meets with the patient's goals.

Management of compartment syndrome after revascularization

The lower extremity muscles reside in compartments, surrounded by fascia and bones. Reperfusion to ischemic muscles can cause cellular edema, resulting in increased compartment pressure. When compartment pressure is >30 mm Hg, there is capillary and venule compression that leads to malperfusion of the muscle; this is compartment syndrome. Fasciotomy is indicated when the compartment pressure increases. Measurement of intracompart-ment pressure is not always easily accessible. In such cases, evaluation for fasciotomy is prompted by development of increased pain, tense muscle, or nerve injury. Fasciotomy should be considered for patients with Category IIb ischemia for whom the time to revascularization is >4 hours.

Treatment of the Results

Assessment of the comparative effective-ness of catheter-based thrombolysis versus open surgery is complicated by variable definitions of ALI in this literature [1]. Four RCTs comparing catheter-based thrombolysis to surgery, [43-46] as well as a meta-analysis [47], have demonstrated similar limb salvage rates between the 2 approaches but better survival with catheter-based therapy. The survival advantage of catheter-based therapy may be at least in part attributable to multiple comorbidities found among the population of patients who present with ALI. Increased comorbidities are likely to contribute to increased perioperative risk. Several of the RCTs included patients with relatively chronic ischemia. Acuity and severity are both factors in the decision to consider thrombolysis. [43-46]. Regarding Limb loss and survival, Ashraf G. Taha, the overall 30-day amputation rate was significantly higher with OR (13.5%) than with ER (6.5%; P ¼ .02; Table III and Fig 1). The overall mortality rates (Fig 2) were significantly lower with ER than with OR at 30 days (5.4% vs 13.2%; P ¼ .012), 1 year (12.9% vs 33.8%; P < .001), and 2 years (18.7% vs 40.5%; P < .001).

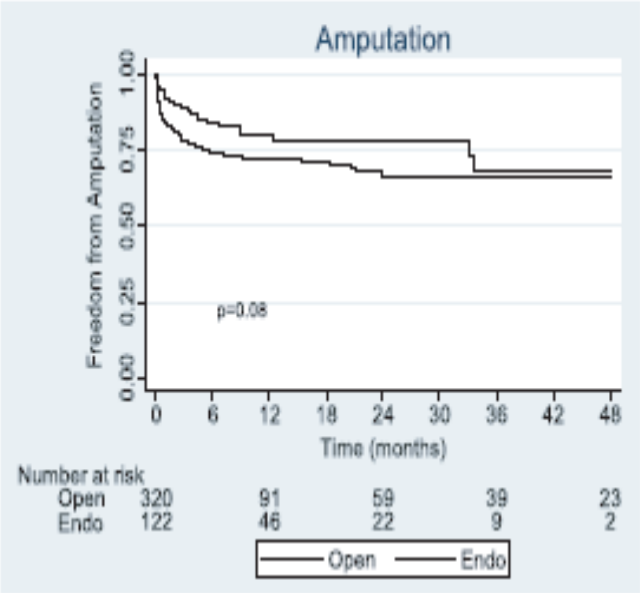

Fig 1. Kaplan-Meier survival curve: Amputation-free survival (limb-based analysis).

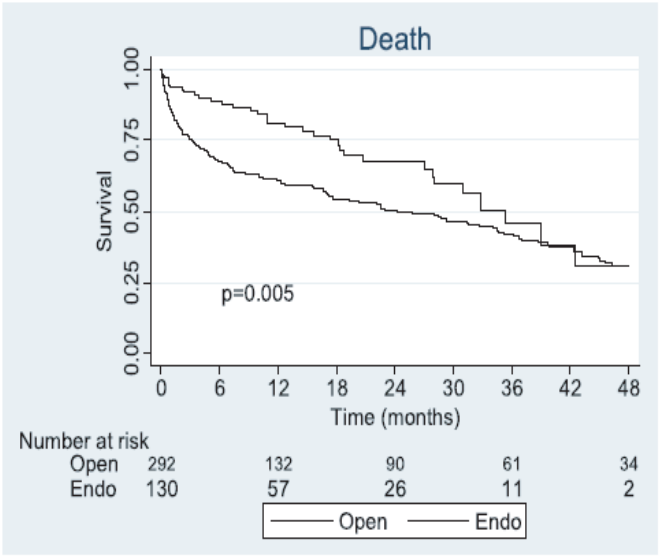

Fig 2. Kaplan-Meier survival curve: Survival analysis (patient-based analysis).

Table V: Outcome of Patients Treated with Initial Thrombolytic Therapy or Primary Operation for Acute Limb Ischemia [3]

Series	Number of Patients	Period (months)	THROMBOLYTIC THERAPY Amputation (%)	Death (%)	PRIMARY OPERATION Amputation (%)	Death (%)
University of Rochester [43]	114	12	18	16	18	42
STILE Trial [44]	393	6	12	6.5	11	8.5
TOPAS Trial-II [45]	544	12	15	20	13.1	17

Table VI: amputation, Mortality, and Long-term Limb Salvage for Open Surgery for Acute Limb Ischemia **[3]**

Series	Year	Number of Patients	RESULTS Amputation (%)	Mortality (%)	Limb Salvage
Campbell et al [34]	1998	474	16	22	Not reported
Nypaver et al [35]	1998	71	7	10	62% at 1 yr
Pemberton et al [36]	1999	107	12	25	75% at 2 yr

Particular Case: Upper Limb Ischemia[3]

A number of significant differences exist between acute ischemia of the arm and that of the leg. Patients with acute arm ischemia tend to be, on average; about 4 years older than those with acute leg ischemia (mean age, 74 years). Arm ischemia is seldom limb threatening, and treatment decisions are usually less urgent. [48,49].
The main reason for treating arm ischemia is to prevent late complications such as exercise-induced arm fatigue and pain [50]. Most arm ischemia is due to cardiac embolism. Rare causes of arm emboli include thoracic outlet syndrome and proximal subclavian artery aneurysm. Atherosclerosis is rare in upper limb arteries, and collateral vessels usually prevent acute limb ischemia when atherosclerosis is present. Patients with upper limb ischemia often present with a cold feeling and numbness, rather than pain in the arm. The diagnosis of ALI in the upper extremity is clinical and can be confirmed by duplex ultra

sonography. The arm often improves after initial anticoagulation, and decisions about whether to perform embolectomy can be difficult. Up to 50% of patients have late symptoms of arm pain if untreated. Consequently, there should be a low threshold to undertake embolectomy if there is doubt about limb viability [50]. A small number of patients present with class IIb critical ischemia and require urgent surgical intervention [49] Failed surgery in this situation risks ischemic contracture or even arm amputation on occasion. The threat to the arm is generally low, but up to 20% of patients with acute arm ischemia do not survive the acute event, usually owing to cardiac complications[51] As with acute leg ischemia, there is a high attrition rate after successful treatment; only 60% of patients survived 3 to 5 years in one typical series. [51]

Conclusion

ALI is a surgical and radiological emergency. Prompt clinical evaluation and appropriate use of the available management options can result in good limb salvage rates. If the limb demons-trates clinical signs of irreversible ischemia, time should not be wasted at attempted revasculari-zation; saving life over limb is paramount.

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