Revascularization of Acute Limb Ischemia

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ABSTRACT

Acute limb ischemia (ALI) is a medical emergency which can lead to loss of limb and even death. The outcomes are depending on the immediacy and completeness of revascularization or reperfusion. Generally, the considered a golden period in the management ALI is 6 hours. Unfortunately, the handling of patients with ALI is often too late. Currently there are several methods of revascularization such as thrombolysis (catheter directed thrombolysis), percutaneous and open surgical mechanical thrombectomy. The selection method where is the best revascularization remains controversial. Some research suggests that outcomes did not differ between thrombolysis and surgical therapy.

INTISARI


Introduction

Acute limb ischemia (ALI) is a condition where there is a sudden blockage of blood flow in the lower extremities that can threaten the viability of the extremities and occur within a period of 2 weeks. This situation is distinguished from critical limb ischemia, which is considered a chronic condition, that is, if the symptoms of ischemia last more than 2 weeks.1,2 It is a medical emergency that can cause loss of the lower extremities even to death. The patient’s output depends on the speed and perfect reperfusion of the affected extremity.3 Until now, there has been no definite terminology for how long ischemia affects the outcome. Generally, the considered golden period in the management of ALI is 6 hours. But delays in handling ALI are still common, around 45-66% of cases.3,4,5,6

The incidence of ALI is estimated to be around 140/1 million population/year. The risk of amputation within 30 days is around 10% - 30% with a mortality of 15-20% despite using the latest endovascular techniques and thrombolysis.2 At present, there are several methods of revascularization such as thrombolysis (catheter directed thrombolysis), PMT and open surgery. The choice of which revascularization method is the best is still a matter of controversy.2,7

Discussion

Etiology

The main causes of ALI are embolism (30%) and thrombosis (60%). The etiology of ALI as resource of the embolism frequently comes from cardiac chambers because of arrhythmia as atrial fibrillation. Most of the embolism originates from the heart due to valvular disease, prosthetic valves, and mural thrombus in
myocardial infarction or left ventricular dilatation. Noncardiac sources include arterial aneurysms, atherosclerotic plaque rupture, post-endovascular procedures, and paradoxical embolism from veins or vascular trauma. Whereas acute thrombosis can occur due to in situ thrombosis may cause by plaque rupture or migration of the path towards the distal part. Arterial thrombosis is usually associated with advanced atherosclerosis.9,10

Arterial embolism has sudden clinical symptoms and is more severe than thrombosis. Embolism will usually clog arteries that were previously healthy, whereas thrombosis usually has formed collateral blood vessels due to chronic ischemia so that clinical manifestations are not as severe as embolism.11,12,13,14 Clinically the difference between the two is shown in table 1.

**Table 1.**

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Embolism</th>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>A few seconds - minutes</td>
<td>A few hours-days</td>
</tr>
<tr>
<td>Blockage</td>
<td>Total</td>
<td>There is collateral</td>
</tr>
<tr>
<td>Multiple locations</td>
<td>Total</td>
<td>Rarely</td>
</tr>
<tr>
<td>Upper limb involvement</td>
<td>Up to 15%</td>
<td>Rarely</td>
</tr>
<tr>
<td>The source of embolism</td>
<td>Frequent (25%)</td>
<td>There is no</td>
</tr>
<tr>
<td>History of claudication</td>
<td>There is</td>
<td>There is</td>
</tr>
<tr>
<td>Palpate the arteries</td>
<td>There is no</td>
<td>Hard</td>
</tr>
<tr>
<td>Contralateral arterial pulsation</td>
<td>Supple</td>
<td>Weak / non-existent</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>existent</td>
</tr>
</tbody>
</table>

**Pathophysiology**

Blockage in the arteries will cause tissue perfusion disorders and trigger the formation of thrombus which can then expand. Cells that run into ischemia will have anaerobic metabolism resulting in acidosis and reduced formation of adenosine triphosphate (ATP). The Na-K-ATP pump cannot work so that sodium and water retention in the cell occurs. The calcium pump is also disrupted so that intracellular calcium levels will increase. Increased intracellular calcium activates cytosolic enzymes that can trigger cell damage. Furthermore, the release of toxic substances into the circulation is due to damage to cell membranes. Precapillary arteriole cells also run into swelling so that the distal lumen, capillaries and venules become narrow. Finally, toxic metabolite products will be retained in the network that ischemic. The state of acidosis in cells causes chromatin clumping which eventually leads to cell death.15,16,17,18,19

Damage to muscle tissue is the most important aspect in the process of reperfusion injury because muscle is the main constituent tissue of the limb. Skeletal and nerve muscles are the most vulnerable tissues to ischemia. Histological changes occur within 4-8 hours of ischemia in both tissues.19

Reperfusion of ischemic extremities can cause a paradoxical reaction known as ischemia-reperfusion injury. This situation is caused by the formation of oxygen free radicals and neutrophil migration due to the return of blood flow to the tissue that ischemic. The local effects of reperfusion are compartment syndrome, necrosis and impaired muscle function. While the systemic impact is known as myonephropathic syndrome which is characterized by acidosis, hyperkalemia which can subsequently cause cardiac arrest, increase in creatine phosphokinase (CPK) and serum glutamic oxaloacetic transaminase (SGOT), myoglobinemia-myoglobinuria which can cause kidney failure, activation of the coagulation cascade, accumulation of SGOT, myoglobinemia-myoglobinuria which can cause kidney failure, activation of the coagulation cascade, accumulation of SGOT, myoglobinemia-myoglobinuria which can cause kidney failure, activation of the coagulation cascade, accumulation of SGOT, myoglobinemia-myoglobinuria which can cause kidney failure, activation of the coagulation cascade, accumulation of extracellular and acute pulmonary insufficiency.12,13,20

**Diagnosis**

Acute limb ischemia is a clinical diagnosis. It is clinically recognized by the 6 P mark, namely pain, pallor, pulselessness, paresthesia, paralysis and poikilothermic. The diagnosis of ALI is based on history, physical and supporting examination.4,14

History of illness includes complaints related to ischemic conditions in the lower extremities and disease background. Pain and dysfunction are the main complaints of ALI patients. Initially the pain is felt in the distal area of the lower extremity and then extends to the proximal area, but in the advanced stages the pain intensity will decrease with the loss of nerve sensibility. To look for background disease, it is necessary to ask whether there is a history of intermittent claudication, history of interventions due to blood flow disorders, history of heart disease or aneurysm and also risk factors for atherosclerosis such as smoking history, dyslipidemia and diabetes mellitus.2,17

Physical examination includes local conditions in the lower extremities and also general conditions related to cardiovascular status and risk of bleeding. At the beginning of ischemia, the skin appears pale due to arterial vasospasm in the distal occlusion area. A few hours later the skin will appear bluish that disappear with pressure, because vasospasm begins to decrease so that the blood vessels are filled with deoxygenated blood. In the later stages the bluish color does not disappear with pressure, because there is coagulation of blood in the branches of the arteries. The palpation of the extremities will feel cold. Muscles that feel hard like wood show muscle infarction with edema and are a sign of irreversible ischemia. Examination of the lower extremities should also be seen for signs of chronic ischemia such as skin atrophy, hair loss and nail thickening.17,21,22

Palpation of peripheral arteries varies in accuracy. Palpable arterial pulses are suggestive of ALI but are not diagnostic, whereas palpable pulsations do not exclude
ALI diagnosis. Therefore, it is necessary to use duplex ultrasound to get objective results.\textsuperscript{14,23} Examination of arterial pulsation in the contralateral lower limb can be used to estimate the etiology of the blockage. Weak pulsation in the contralateral lower limb indicates a background of chronic arterial obstructive disease and means the possibility of thrombosis as a cause of acute ischemia. Whereas arterial pulsation in the contralateral lower extremity is normal, the probable cause of arterial obstruction is embolism.\textsuperscript{17} An arterial pulsation examination can also be used to estimate the location of the blockage. For example, a patient with palpable femoral artery pulsation, while popliteal artery pulsation is not palpable, may be a blockage in the femoral artery segment. If the femoral artery pulsation is not palpated, there is a possibility that the disturbance is above the inguinal ligament.\textsuperscript{14,23}

To prove the existence of hypoperfusion in the limbs a Buerger test can also be performed. In normal people the legs can be raised to 90 degrees, and the toes remain red. In limbs that have ischemia removal of 15-30 degrees already causes pale and if the legs are positioned lower limbs will have reactive hyperemia. The angle at which the limb turns pale when the leg is raised is called the Buerger angle.\textsuperscript{23}

Neurological examination is intended to assess motor and sensory function. Numbness or paresthesia is an early sign of a nervous breakdown due to ischemia. Severe impairment of sensory and motor functions is a sign of advanced ischemia.\textsuperscript{17}

A condition that resembles ALI to think about is Blue toe syndrome. This situation is caused by the presence of atheroembolism in the form of cholesterol microcrystalline debris from arterial plaque that has ruptured in the proximal region. As a result, local ischemia occurs in the toes that are marked bluish, cold and pain that arises suddenly but on palpation still obtained distal arterial pulsation. This situation is a risk that episodes of embolism will occur in the future.\textsuperscript{14,17}

Societies of Vascular Surgery/International Society of Cardiovascular Surgery (SVS/ISCVS) make the ALI classification into 4 categories based on the severity of the disease, as in table 2.

### Differential Diagnosis

The differential diagnosis needs to be known because there are several conditions that resemble ALI which are contraindicated anticoagulant administration. The differential diagnosis of ALI includes non-vascular musculoskeletal trauma, arterial trauma, radiculopathy (spinal stenosis, vertebral disc herniation), popliteal cysts, phlegmasia cerulea dolens, aortic dissection and compartment syndrome. Systemic disorders such as cardiogenic shock or sepsis can also manifest as ALI. Drugs such as cocaine and vasopressors can also cause severe vasospasm so that the extremities have acute ischemia.\textsuperscript{24,16}

<table>
<thead>
<tr>
<th>Category</th>
<th>Description Prognosis</th>
<th>Clinical</th>
<th>Doppler signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Threatened/ not threatened immediately</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>II</td>
<td>Marginal / can be saved if treated immediately</td>
<td>Minimum /</td>
<td>Often(-) (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediately / can be saved if revascularization immediately</td>
<td>Rest pain</td>
<td>Alms /</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>moderate</td>
</tr>
<tr>
<td>III</td>
<td>Irreversible / extensive tissue death or permanent nerve damage</td>
<td>Progressive /</td>
<td>Progressive /</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anesthesia</td>
<td>paralysis</td>
</tr>
</tbody>
</table>

**Table 2. Classification of the severity of ALI based on SVS / ISCVS**

**Supporting examination**

Supporting examination that need to be done in ALI patients include routine blood, blood chemistry, coagulation function (prothrombin time, partial thromboplastin time), CKP and electrocardiogram.\textsuperscript{4,24} Arteriography with contrast is still the gold standard for the diagnosis of ALI if there are no contraindications such as kidney disorders or contrast allergy.\textsuperscript{23} Arteriography can distinguish thrombosis from embolism. Embolism appears as filling defect, firm round border with meniscus sign, other blood vessels are normal, no collateral circulation is obtained and multiple filling defects are present. While thrombosis appears as a clear non-circular border and the presence of atherosclerosis and collateral blood vessels.\textsuperscript{17}

Alternative imaging examinations other than arteriography are duplex ultrasonography, computed tomographic angiography (CTA) and magnetic resonance angiography (MRA). Duplex ultrasonography (DUS) can be used to determine the location of obstruction, assess plaque morphology, stenosis, dissection and thrombus. The role of DUS for the diagnosis of ALI is very important because DUS is the first imaging choice to assess ALI. It is widely available, has a low cost, is non-invasive, non-irradiant and it takes a relative short time to perform. The sensitivity of this tool is around 80-98% and the specificity is 89-99%. CTA and MRA are less invasive than conventional arteriography. CTA has a sensitivity of 89-99% and a specificity of 83-97%, while MRA has a sensitivity of 92-99.5% and a specificity of 64-99%.\textsuperscript{5,14,25}

Echocardiographic examination in ALI patients is useful for finding the source of embolism from the heart. If transthoracic echocardiography is not found the source of embolism and the suspected cause of ALI is embolism then it should be done transesophageal echocardiography.\textsuperscript{26,27,28} Echocardiography can also see the possibility of paradoxical embolism.\textsuperscript{29}
Management

Initial ALI therapy aims to prevent thrombus expansion and worsening ischemia. This can be achieved by administering intravenous unfractionated heparin (UFH) immediately after the diagnosis of ALI is based on clinical appearance. Heparin therapy should not be postponed for reasons of waiting for investigations. After initiation of heparin therapy further therapy depends on limb viability as shown in figure 1. Antplatelet therapy is also recommended to be given immediately with aspirin 75-325 mg. \(^{2,14,21}\)

![Algorithm for the management of acute limb ischemia.](image)

**Figure 1.** Algorithm for the management of acute limb ischemia.\(^{2}\)

Category I – Viable; Category IIA - Marginally Threatened; Category IIB - Immediately Threatened; \(\alpha\) - Confirming either absent or severely diminished ankle pressure/signals; *In some centers imaging would be performed.

Revascularization in ALI can be done with thrombolysis or surgical therapy.\(^{11}\) Percutaneous mechanical thrombectomy (PMT) is another modality that can be used to overcome the limitations of thrombolysis.\(^{2,21}\)

Thrombolysis

Definition of thrombolysis in ALI is generally intraarterial thrombolysis with endovascular techniques or CDT (Catheter Direct Thrombolysis). Results confirm the high direct technical success rate of CDT and the high percentage (88.5%) of patients survived without amputation within 30 days, although major complications are a great disadvantage of the method.\(^{43}\) Systemic thrombolytic administration has been abandoned because of the greater risk of bleeding.\(^{2,20}\) Several studies report the use of intravenous thrombolysis is quite safe with a successful reperfusion of about 76-77% without major bleeding complications.\(^{31,32}\) But the number of samples in these studies is small.

Thrombolytic drugs work indirectly to destroy fibrin by converting plasminogen to plasmin.\(^{33}\) Streptokinase is the first indirect plasminogen activator used for intrarterial thrombolysis, but now its use has been restricted in America because of its lower efficacy and higher bleeding risk compared to other drugs. In addition, streptokinase has the potential to trigger allergic reactions. Urokinase, a direct plasminogen activator is also not used in America because of production reasons.\(^{2,24}\)

There are currently several thrombolytic drugs such as alteplase a recombinant tissue plasminogen activator (rtPA) derived from human tissue plasminogen activator (tPA) clones and those derived from tPA genetic engineering such as reteplase (rPA) and tenecteplase (TNK). These drugs have different half-lives, specificity for fibrin (differences in activity against fibrin bound plasminogen compared to circulating plasminogen) and affinity for fibrin (stability of bonds to fibrin). This difference is a consideration for drug selection in the thrombolysis / CDT action. Theoretically rtPA can penetrate into the thrombus better than alteplase, an rtPA so that thrombolysis time is faster and consequently the risk of bleeding is smaller. TNK is fibrinolytic which has the highest fibrin specificity. In theory TNK has less effect on plasminogen activation in circulation and thrombolysis time is faster than rtPA or rtPA because it is more resistant to plasminogen activator inhibitor-1. But the level of clinical evidence is still weak.\(^{1,33}\)

Current thrombolytic drugs have several limitations. On average these drugs take about 24 hours to restore blood flow so they are not used in patients with category IIB. Besides, systemic effects (lytic state) due to hypofibrinogenemia can still occur despite using fibrin specific drugs and given locally. Therefore, thrombolytic administration must consider several contraindications such as cerebrovascular attack, active bleeding, intracranial injury and other conditions with a risk of bleeding.\(^{14,33}\)

Post heparin thrombolysis should be given to prevent retrombosis of blood vessels and prevent thrombosis around the catheter. When given with thrombolytic agent, heparin is given in low doses (subtherapy) because in the presence of fibrinogen degradation products bleeding will be easier. Usually a dose of 200-500 units per hour is used with a PTT target of 1.25-1.5 times the control.\(^{14,24,30}\)

Percutaneous Mechanical Thrombectomy (PMT)

PMT is especially useful in patients who have contraindications to thrombolysis and can be used as adjunctive therapy for incomplete thrombolysis. This tool can also reduce the mass of the thrombus (debunking) before thrombolysis so that the reperfusion time is faster.\(^{20}\) Some tools used include simple aspiration type catheters, rotational or hydraulic recirculation devices (Helix, Angiojet, Trellis® ) and ultrasound enhanced thrombolysis (EkoSonic®).\(^{21}\) This method resulted in amputation free survival of 94.7% with a mortality of 29.6% in 5 years.\(^{34}\)

Percutaneous transluminal angioplasty

Percutaneous transluminal angioplasty (PTA) is useful for repairing arterial obstruction due to atherosclerotic processes. However, the results of infra-inguinal artery blockage are less satisfactory. The risk of perforation and distal embolism is increased when PTA is used on long obstruction. Angioplasty with conventional old plain balloon angioplasty (POBA) has a risk of occurrence dissection, acute elastic recoil, restenosis due to intima hyperplasia and negative remodeling. Several new technologies have been developed to overcome the...
limitations of PTA, including by cutting or scoring balloons and cryoplasty.35

Until now, the installation of drug-eluting stents for peripheral arteries has not been approved in America because of the high restenosis rate (75%), while the use of nitinol stents has been approved by the Food and Drug Administration (FDA). Nitinol stents are a mixture of nickel and titanium which have super elastic properties (can return to their original form if external pressure is removed) and have a thermal shape memory (return to the previous form on heating). Therefore, this tool can be used for areas that do not allow flexion or torsion movements such as the superficial femoral artery or the popliteal artery.35

Surgical revascularization

Indications for surgical revascularization are category IIb ischemia. Surgery can be a thromboembolectomy with a balloon catheter (Fogarty) or bypass surgery. Surgical strategy is determined by the etiology of arterial occlusion (embolism or thrombosis) and anatomical features of blood vessels.7

The addition of intraoperative thrombolytic drugs can be beneficial because residual thrombus is often obtained after surgical thromboembolectomy (36%) and thrombus in small blood vessels is often unreachable.36 Intraoperative angiography can be used to assess the success of reperfusion.37

Until now, there is still controversy over which reperfusion therapy will be chosen, thrombolysis or surgery. Usually category Ila and IIb are used as a limit to determine the type of reperfusion therapy.7,36 Some random studies like Rochester study, Thrombolysis or peripheral arterial surgery (TOPAS) and Surgery versus thrombolysis for ischemia of the lower extremity (STILE) showed no difference in mortality and amputation free survival in 30 days on thrombolysis therapy and surgical therapy.37,38,39 But these studies have different characteristics of the study population such as the duration and severity of ischemia, the type of thrombolytic used and the length of follow-up.2,17

Usually the selection of revascularization therapy is based on the severity of ischemia, etiology, location of the occlusion and the general condition of the patient. Thrombolysis is the treatment of choice for ALI patients with categories I and IIa (class I, Level of Evidence: A), whereas patients with progressive ischemia or category IIb are indicative of surgical revascularization. Thrombolysis therapy can also be considered in category IIb (class IIb, Level of Evidence: B). Infrageninal or distal arterial thrombolysis has less satisfactory outcomes than iliofemoral or proximal. In cases of embolism, surgical therapy or thrombolysis can be used whereas in cases of thrombosis it requires more complex procedures such as bypass surgery or POBA.2,21,40

Prognosis

The risk of amputation of ALI patients within 30 days is about 10% - 30% with a mortality of 15-20%. Some factors that influence outcomes include old age, duration of ischemia, severity of ischemia, etiology of blockage, and accompanying diseases such as diabetes mellitus, history ischemic heart disease and heart failure.3,5,41,42

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Conclusion

Acute limb ischemia (ALI) is a vascular emergency with high morbidity and mortality. Early recognition and immediate revascularization are the keys to success management of ALI. Heparinisation therapy must be given immediately when a clinical diagnosis has been established without waiting for the results of investigations. Until now there has been no evidence of differences in the efficacy of thrombolysis with surgical therapy. Consideration of the choice of revascularization therapy is based on the severity of ischemia, etiology, location of occlusion and general condition of the patient.

References


