

# Reperfusion of Delayed Acute Occlusive Limb Ischemia: Is It Worthwhile?\*

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## Abstract

Delayed reperfusion of acute occlusive limb ischemia causes local and systemic serious consequences and is the main cause of morbidity and mortality in these patients. The aim of this study was to examine the outcome and risk factors of reperfusion injury in such cases. **Patients and Methods:** Retrospective review of all cases presented, to King Fahd Hospital of University, with acute occlusive limb ischemia more than 12 hours was performed between June 2004 and November 2012. Grades of ischemia, extremities, co-morbidities, morbidities and mortality were recorded. **Results:** During the study period, 92 patients were included, 47 (51%) were embolic and the rest was thrombotic. On admission, 15 patients had grade III ischemia, 68 had grade IIb, 8 had grade IIa and 1 had grade I. Four patients died (4.3%) and 15 (16%) patients had amputation. The risk factors of amputation were age ( $p = 0.031$ ), extremity (lower limb 21% vs. Upper limb 0%,  $p = 0.019$ ), cause of ischemia (thrombotic 24% vs. embolic 8.5%,  $p = 0.049$ ) and grade of ischemia ( $p = 0.001$ ). **Conclusion:** Delayed reperfusion of acute occlusive ischemia carries acceptable morbidity and mortality and could be performed even in irreversible ischemia. The risk factors of amputation are age, lower limb ischemia, thrombosis and grade III ischemia.

## Keywords

Acute Limb Ischemia, Thrombosis, Embolism, Delayed Ischemia

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## 1. Introduction

Acute limb ischemia (ALI) is sudden decrease in limb perfusion causing a potential threat to limb viability. Presentation is normally up to 2 weeks following the acute event [1]. It is usually due to acute occlusion of ar-

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terial blood vessel by a thrombus or emboli. Reperfusion of a limb after prolonged ischemia causes cytokine liberation, leucocytes activation, increased expression of adhesion molecules, and activation of complement cascade and formation of toxic oxygen metabolites. Reactive oxygen intermediates may cause secondary cellular damage not only in the reperfused extremity but also at remote organ sites [2]. Delayed revascularization causes also liberation of ischemic metabolites, myoglobulinemia and myoglobunuria [3]. Such complications increase morbidity and mortality in these patients [2] [3]. The aim of this study was to examine the outcome and risk factors of reperfusion injury in such cases

## 2. Patients and Methods

Retrospective review of all cases presented, to our vascular unit, with acute occlusive limb ischemia more than 12 hours was performed. Revascularization in the first 12 hours after the onset of symptoms gives the best results. The vascular unit, King Fahd Hospital of University, Alkhobar, Saudi Arabia covers a wide area. This resulted in a delay in the management of most of cases of acute ischemia. The study was approved by local ethical committee. All hospital records of acute limb ischemia treated between June 2004 and November 2012 were reviewed. Patients with ischemia less than 12 hours, vascular graft occlusion, acute trauma or who refused revascularization were excluded from the study. Grades of ischemia (Viable I, marginally threatened IIa, immediately threatened IIb and Irreversible III) were reported according to clinical categories of acute limb ischemia [4]. Preoperative diagnosis was based on history, physical examination  $\pm$  CT angiogram. Distinguishing embolism from thrombosis was mostly based on: prior history of intermittent claudication or rest pain, a known embolic source such as cardiac arrhythmias, pulse and Doppler examination in the unaffected limb and CT angiogram. All patients had CT angiogram unless there was renal impairment or there was expected delay from the procedure. Patient demographic and co-morbidities such as ischemic heart disease, renal impairment, and cerebrovascular disease were recorded.

All patients had perioperative heparin as an intravenous bolus of 100 U/kg body weight followed by an intravenous drip to maintain an activated partial thromboplastin time of 2 - 2.5 times the control. In cases of embolism, femoral arterial thromboembolectomy was performed followed by on table angiogram. Thrombolysis was done if a residual thrombus was revealed. In cases of acute thrombosis, surgical bypass or endovascular intervention was performed. The choice of intervention depends on the available expertise and the clinical category of the acute ischemia. Four-compartment fasciotomy was performed through an anterolateral and a posteromedial skin incisions in all cases with grades IIb or III or patients who developed compartment syndrome.

Postoperative, warfarin was given as oral anticoagulation therapy long term if necessary. The target international normalized ratio (INR) was maintained at 2 - 3. Aspirin at a dose of 81 mg/d was initiated after the treatment to be continued indefinitely. Morbidities and mortality were recorded within 30 days of hospital admission. The patients were divided into 2 groups; group I (limb was salvaged) and group II (limb was amputated).

## Statistical Analysis

Comparison between prevalence of risk factors in both groups I and II was done. Data for groups were summarized either as the mean  $\pm$  standard deviation (SD) or as percentage of the risk factors. Differences between the groups were tested for statistical significance using t-test, chi-square test or Fisher's exact test as appropriate. Significance was set at  $p < 0.05$  for all comparisons. Statistical analyses were performed using SPSS 15 software (Chicago, USA).

## 3. Results

During the study period, 92 patients were included, 60 (65%) patients were men and 32 were women. Mean age (years  $\pm$  SD) was  $46 \pm 11.62$  (range 21 - 81 years) (Table 1). The cause of ischemia was embolic in 47 patients (51%) and the rest was thrombotic. Atherosclerotic disease was the most common cause and the heart was the most common source of acute arterial embolism (Table 2). Most of the cases of embolism in patients with arrhythmia were due to noncompliance to the anticoagulant therapy. On admission; 15 patients had grade III ischemia, 68 had grade IIb, 8 had grade IIa and 1 had grade I. Fasciotomy was performed in 85 (92%) patients. At 30 days of hospital admission, four patients died (4.3%). One had extensive myocardial infarction, one had stroke and two had multiple organ failure.

Complication rate was high (**Table 3**). There was a transient rise of serum creatinine postoperative in all cases. Temporary hemodialysis was required in 16 (17%) of them. None required permanent hemodialysis. Fifteen

**Table 1.** Patients characteristics.

Variable	Number (%)
Age; Mean ( $\pm$ SD)*	46 $\pm$ 11.62
Sex; Male/Female	60/32
Smoking	50 (54%)
Diabetes	69 (75%)
Hypertension	33 (36%)
Dyslipidemia	60 (65%)
Renal failure	4 (4%)
Ischemic heart disease	39 (42%)
Cerebrovascular disease	2 (2%)
Site of occlusion: UL/LL	21/71
Cause of acute ischemia: Embolic	47 (51%)
Thrombotic	45 (49%)
Degree of ischemia: Grade I	1 (1%)
Grade IIa	8 (9%)
Grade IIb	68 (74%)
Grade III	15 (16%)

\*SD = Standard Deviation. Grade I; Viable, Grade IIa; Marginally threatened Grade IIb; Immediately threatened, Grade III; Irreversible [11].

**Table 2.** Etiology of embolism.

Etiology	Number (%)
Cardiac	35 (74%) patients
Arrhythmia	25
Valvular disease	4
Post-myocardial infarction	6
Extra-cardiac disease	8 (17%)
Aortic arch atherosclerosis	6
Abdominal aortic atherosclerosis.	2
No cause was identified	4 (9%)

**Table 3.** Complications.

Etiology	Number (%)
Surgical site infection	18 (20%)
Renal failure required temporary hemodialysis	16 (17%)
Amputation.	15 (16%)
Neurogenic: Foot drop	14 (15%)
Transient liver impairment	13 (14%)
Myocardial infarction	8 (9%)

patients (16%) had amputation. Twelve had above knee amputation. Of these 12 cases, 6 had ileofemoropopliteal occlusion and they were expected to have high knee above amputation if no intervention was performed. Three had below knee amputation, all of them had femoropopliteal occlusion and they were expected to have above knee amputation if no intervention was performed. In grade III ischemia, 8 had amputation and the rest had foot drop which mostly improved with physiotherapy. The risk factors of amputation were age ( $p = 0.031$ ), lower limb ischemia ( $p = 0.019$ ), thrombosis ( $p = 0.049$ ) and grade III ischemia ( $p = 0.001$ ) (**Table 4**).

#### 4. Discussion

ALI is a vascular emergency, associated with significant morbidity and mortality. Amputation rate is ranging from 7.5% [5] to 14.3% [6]-[8] compared to 16% in the present study. The exclusion of early ischemia in our study may explain this higher amputation rate. Mortality rate is ranging from 8.5% [5] 10.5% [6] [7] [9] compared to 4.3% in the present study. The younger age group in the present study (mean age in ours was 46 years compared 64 - 70 years in others [5] [9]) may explain this difference. Age is a significant risk factor in the mortality rate [5] [10].

During the last 3 decades there was increased incidence of atherosclerosis and this has resulted in changing patterns in the etiology of acute lower limb ischemia from mainly emboli to mostly thrombotic [11]. However, the present study and others [5] [9] showed that embolism still out numbers thrombotic occlusion. This may be due to noncompliance of our patients with arrhythmia to anticoagulant. Nevertheless, all recent studies [5] [11] including ours, showed that the leading cause of embolic occlusion nowadays is atherosclerotic disease. The majority (74% present study, 80% [12] - 91% [5]) of arterial emboli originated in the heart.

Incidence of grade III acute ischemia is 16% in the present study compared to 10% in other studies [1] [5]. The exclusion of early ischemia in our study may explain this higher incidence. The standard treatment for this category (irreversible ischemia) is major amputation or conservative treatment [1]. However, it is reported that patients presenting very soon after the onset of ischemia with grade III findings, a functional limb may actually be salvaged occasionally if revascularization is accomplished immediately [5] [13] [14]. Amputation rate in this category varies from 31% [5] to 53% in the present study. The lower rate in the former study may be explained by that most of these cases were due to embolic occlusion.

**Table 4.** Risk factors for amputation.

	Group1 (Salvage)	Group 2 (Amputation)	P value
Age; Mean ( $\pm$ SD)*	44 $\pm$ 7.8	69 $\pm$ 9.3	0.031
Sex; Male/Female	51/26	9/6	0.64
Smoking	42	8	0.42
Diabetes	56	13	0.25
Hypertension	26	7	0.34
Renal failure	2	2	0.12
Dyslipidemia	51	9	0.64
Ischemic heart disease	32	7	0.47
Cerebrovascular disease	3	1	0.51
Site of occlusion: UL/LL	21/56	0/15	0.019
Cause of acute Ischemia: Embolic/Thrombotic	43/34	4/11	0.049
Degree of ischemia: Grade I	1	0	0.001
Grade IIa	8	0	
Grade IIb	61	7	
Grade III	7	8	

Reperfusion of limbs after prolonged ischemia causes local and systemic serious consequences and is the main cause of morbidity [2] [3] and mortality [2] [3] [15] in such cases. Therefore, amputation was performed in the presence of acute ischemia presenting late with significant tissue necrosis due to fear of the risk of reperfusion injuries [16] [17]. However, few reports of delayed reperfusion revealed accepted mortality and amputation rates [5] [18]. In present series, the mortality rate was low. Moreover, most of cases which had amputation, there was improvement of its level. In addition, perception of amputation in our community is poor. This might justify the routine attempt of reperfusion of all cases of acute ischemia regardless of duration of ischemia.

The present study revealed that age is a significant risk factor of amputation. However, other studies [5] [9] [10] showed it has insignificant influence. Previous reports [19] showed that extremities had insignificant influence. However, the present study revealed that the lower limb has significant higher amputation rate than the upper limb. Previous studies [8] including ours indicated that thrombosis is a risk factor for amputation. Other studies showed no significant difference between embolism and thrombosis [5]. Grade of ischemia is another risk factor for amputation in the present study and others [5] [8] [10] [19]. Smoking has been shown to be a risk factor in some studies [8]. However, the present study and others [5] did not confirm this finding. Diabetes, hypertension and renal failure had insignificant effect on amputation rate (present study, others [5]).

## 5. Conclusion

In summary, Delayed reperfusion of acute occlusive ischemia carries acceptable morbidity and mortality and could be performed even in irreversible ischemia. The risk factors of amputation are age, lower limb ischemia, thrombosis and grade III ischemia.

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