Plasma creatine kinase indicates major amputation or limb preservation in acute lower limb ischemia

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Objective: **Acutely ischemic limbs are often of uncertain viability. To assist operative management, this study determined prospectively which indicators on admission were the best predictors of major amputation and, conversely, limb preservation.**

Methods: **Data were collected on admission. Presenting complaint, history, clinical assessment, and blood test results, including creatine kinase (CK), were recorded. Surgical procedures were noted—in particular, the presence or absence of major amputation by death or discharge. The setting was a tertiary vascular referral center in a university teaching hospital. Subjects included all patients referred as emergency cases to the vascular unit over an 18-month period who were admitted for inpatient management with acute lower limb ischemia. The main outcome measure was major amputation.**

Results: **A total of 97 patients with acute ischemia were studied prospectively (51 men and 46 women). Twenty-one patients (21.6%) underwent major amputation. Previous vascular surgery ($P = .012$), mottling ($P = .001$), sensory loss ($P = .003$), motor loss ($P = .001$), muscle tenderness ($P < .001$), absent ankle Doppler signals ($P = .008$), neutrophilia ($P = .011$), and increased CK ($P < .001$) were significantly associated with major amputation. If CK was normal, the risk of major amputation was 4.6% (95% confidence interval, 0.0%-9.7%). If CK was increased, the risk was 56.2% (95% CI, 39.1%-73.4%).**

Conclusions: **Specific clinical findings were significantly associated with major amputation. Of these, only CK had a positive predictive value greater than 50%. Plasma CK can assist operative management of acute lower limb ischemia by quantifying prospectively the risk of major amputation or limb preservation on admission. (J Vasc Surg 2007;45:733-9.)**

Appropriate management of acute lower limb ischemia is complicated by a lack of robust clinical indicators that are accurately predictive of outcome. A history of two or more myocardial infarctions, chronic limb ischemia, or prolonged ischemic symptoms is associated with an increased risk of amputation within 30 days in patients presenting after an acute ischemic event.[1] Absent ankle Doppler signals or the presence of a neurosensory deficit is also significantly associated with limb loss over this time period.[2] Increases in plasma creatine kinase (CK) have been detected in femoral venous efflux from ischemic limbs,[3] and patients undergoing amputation for severe ischemia have been noted to have increased CK before surgery.[4] However, no study has addressed the predictive value of normal or increased CK in acute limb ischemia. To investigate such prognostic markers, this study hypothesized that plasma CK on admission would be predictive of major amputation in acute lower limb ischemia. This prospective investigation collected clinical and laboratory data, including CK levels, and explored relationships with major amputation or limb preservation by discharge.

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Competition of interest: none.

Presented in part at the Association of Surgeons of Great Britain and Ireland, Manchester, UK, May 7-9, 2003.

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CME article

0741-5214/$32.00

doi:10.1016/j.jvs.2006.12.050

METHODS

Data were collected prospectively over an 18-month period from 102 patients with signs and symptoms of acute lower limb ischemia admitted as emergency cases to the Department of Vascular Surgery, Royal Infirmary of Edinburgh, United Kingdom.

Study design. Data were collected on admission. The duration of symptoms and history of risk factors, as well as specific disorders that would compromise the interpretation of blood tests, were recorded. An electrocardiogram, neutrophil count, urea, creatinine, bicarbonate, and CK level were obtained on all patients as a matter of routine. Interventions were recorded in addition to subsequent outcomes, in particular the presence or absence of major amputation. All management decisions were made by the admitting consultant after clinical assessment. The consultant had access to standard blood results but no access to CK.

Inclusion criteria. All patients admitted as emergency cases to the vascular unit with new or newly increased symptoms of lower limb ischemia arising over the preceding 7 days were included in the study. To ensure that the data reflected the breadth of patients presenting with ischemic symptoms, all patients, regardless of severity, were included. The term *acute ischemia* is therefore used in the broadest sense throughout this article and includes patients with mild and severe ischemia.

Exclusion criteria. Known unreconstructable disease at the time of admission served to exclude data from analysis. In addition, patients with untreated thyroid disease, acute myocardial infarction, acute stroke, musculoskeletal trauma, or abdominal pain, all of which could substantially alter the interpretation of tests used in this study, were excluded. Patients who were clearly moribund and beyond operative intervention were also excluded. Second and subsequent presentations of the same patient within the study period were also excluded. In each case, these exclusions prevented false correlations between clinical assessments, blood tests, and outcomes.

Data analysis. SPSS version 12.0 (SPSS Inc, Chicago, Ill) was used for all statistical analyses. Associations between categorical variables were examined by using the χ^2 test or Fisher's exact test, where appropriate. Receiver operator characteristic (ROC) curves were produced to investigate the predictive utility of CK on admission. Asymptotic *P* values for the ROC curves were calculated under the nonparametric Wilcoxon statistic assumption.[5] Positive predictive values and false-negative rates for different thresholds of CK were also calculated by standard techniques.

During analysis, no attempt was made to stratify patients into mildly or severely ischemic groups. This approach permitted the most robust comparisons to be made. For example, the disproportionate increase in limb loss in the presence of a specific risk factor could be demonstrated only by the inclusion of the related group in which the absence of the risk factor was associated with disproportionate limb preservation.

RESULTS

Study patients and exclusions. Over the study period, 102 patients presented as emergency cases with new symptoms that had occurred during the week before admission. Two patients were excluded after acute myocardial infarction or stroke was diagnosed. This rendered impossible the interpretation of CK results and potentially altered the operative strategy. Three further patients were excluded as a result of advanced limb ischemia with multiorgan failure. No surgery could be contemplated in these patients. Of the remaining 97 patients, 73 required operative intervention, of whom 60 required limb salvage surgery and 13 underwent primary amputation. Eight underwent secondary amputation. Twenty-five patients (34.2%) were operated on within 24 hours of admission, and a further 20 (27.4%), within the next 24 hours.

Demographics. Table I shows that there was no significant difference in the proportion of men and women (*P* = .258) and no significant difference between the ages at which men and women presented (*P* = .396). Male sex was not a predictor of amputation (*P* = .334).

Inpatient course. The inpatient course for the entire cohort (n = 97) is shown in Table II. Twenty-four patients did not undergo operative intervention, and 17 of these required anticoagulation alone. One was found to have no surgical option after investigation and rapidly died. A second died after amputation was declined. A third required angioplasty. The remaining 21 patients were discharged after full vascular investigation and conservative management. Fifteen of twenty-four had one or more clinical signs associated with an increased amputation risk (Table III). The mean CK ($\log_{10}$ transformed to correct for asymmetry) in this group was 0.48 times the upper limit of normal (95% confidence interval [CI], 0.074-3.09), with a range of 0.13 to 5.81 times normal. Of the remainder, 73 required surgery, of which 21 required primary (n = 13) or secondary (n = 8) amputation.

Table I. Study demographics (n = 97)

Variable	*Data*
Sex	
Male	51
Female	46
Age (y)	
Men	68 (63-77)
Women	73.5 (56-80)
Symptom duration (d)	1 (0-4)
Previous vascular surgery	20
Bypass graft	14
Acute graft blockage	9
Exclusions (n = 5)	
Moribund	3
Acute myocardial infarction	1
Acute stroke	1

Data are n or median (interquartile range).

Table II. Inpatient course

Variable	*n (%)*
No surgical intervention	24 (24.7)
Anticoagulation	17 (17.5)
Angioplasty	1 (1.0)
Surgical intervention	73 (75.3)
Thromboembolectomy ± lysis	41 (42.3)
Revascularization	19 (19.6)
Major amputation (1° and 2°)	21 (21.6)
Deaths in vascular unit	5 (5.2)
Major amputation	3
Amputation planned, consent withheld	1
Disseminated malignancy	1

A total of 81 operations are shown for 73 patients, because 8 patients underwent secondary amputation.

Table IV shows a more detailed description for the 21 patients who underwent major amputation. Thirteen (61.9%) of 21 underwent primary amputation, whereas 8 (38.1%) of 21 underwent amputation after attempted limb salvage. The mean CK of those undergoing primary amputation was 4.29 times the upper limit of normal (95% CI, 0.46-39.8). Of the eight patients who underwent secondary amputation, three had normal CK on admission. One patient presented with acute embolism, received anticoagulation therapy, and developed heparin-induced thrombocytopenia with massive arterial thrombosis. Despite operative intervention, the patient required amputation. A second patient with embolism showed marked cardiorespiratory instability during embolectomy. This patient required a secondary amputation when sufficiently recovered.

Table III. Clinical assessment in acute limb ischemia

Variable	*n (%)*	*Amputation, n (%)*	*P value*
Presenting complaint			
Cold limb	53 (54.6)	12/53 (22.6)	.795
Pain	89 (91.7)	21/89 (23.6)	.195
Numbness	49 (50.5)	13/49 (26.5)	.238
Weakness	23 (23.7)	6/23 (26.1)	.560
New claudication	22 (22.7)	1/22 (4.5)	.064
History			
Smoking	46 (47.4)	9/46 (19.6)	.563
Diabetes	16 (16.5)	2/16 (12.5)	.509
Ischemic heart disease	34 (35.1)	8/34 (23.5)	.772
Hypercholesterolemia	19 (19.6)	7/19 (36.8)	.120
Hypertension	39 (40.2)	8/39 (20.5)	.789
Previous vascular surgery	20 (20.6)	9/20 (45)	.012
Clinical findings			
Cool limb	65 (67.0)	16/65 (24.6)	.433
Reduced capillary refill	44 (45.4)	6/44 (13.6)	.081
Absent foot pulses	83 (85.6)	17/83 (20.5)	.339
Absent ankle Doppler	57 (68.7)	17/57 (29.8)	.008
Mottling	38 (39.2)	15/38 (39.5)	.001
Muscle tenderness	31 (32.0)	14/31 (45.2)	<.001
Motor loss	31 (32.0)	13/31 (41.9)	.001
Sensory loss	51 (52.6)	17/51 (33.3)	.003

The number and percentage demonstrating pathologic findings is shown, along with the number of patients (%) demonstrating the abnormality who underwent amputation. The *P* value (from χ^2 or Fisher's exact tests) demonstrates the relationship with amputation.

Table IV. Management before major amputation (n = 21)

Variable	*n (%)*
Immediate management	
Anticoagulation	8 (38.1)
Imaging	8 (38.1)
Diagnosis	
Embolism	3 (14.3)
Thrombosis in situ	12 (57.1)
Graft occlusion	6 (28.6)
Operative strategy	
Thromboembolectomy ± on-table lysis	5 (23.8)
Formal revascularization	3 (14.3)
Primary amputation	13 (61.9)
Secondary amputation	8 (38.1)

Primary interventions for patients who underwent secondary amputation (n = 8) are shown under operative strategy.

The third patient experienced widespread embolization during coronary angiography and underwent laparotomy and bilateral femoral embolectomy with thrombolysis. However, one foot progressively developed irreversible ischemia and necessitated below-knee amputation on day 11.

Of the remaining five patients who had secondary amputation, all had abnormal CK and underwent initial limb salvage surgery. One of the 2 with CK greater than 10 times normal underwent emergency revascularization followed by secondary amputation within 24 hours. The other underwent urgent limb salvage surgery but was found unexpectedly to have dead muscles and so underwent amputation directly. A third patient, with CK 7.78 times the upper level of normal, also underwent exploratory surgery before amputation under the same anesthetic. The remaining two patients had admission CK levels 4.18 and 1.67 times normal. These patients had embolectomy and fasciotomies or thrombectomy of an acutely occluded common femoral aneurysm, respectively, but ultimately required above-knee amputations for irreversible ischemia.

History and examination. Table III demonstrates that no specific presenting complaint was significantly associated with amputation in acute limb ischemia. It is notable that new-onset claudication (P = .064) attained near-significance as a predictor of limb preservation. Previous vascular surgery was identified as significantly associated with amputation (P = .012). Mottling (P = .001), muscle tenderness (P < .001), motor loss (P = .001), and sensory loss (P = .003) were significantly associated with amputation. Absent ankle Doppler signals were also significantly associated with amputation (P = .008); however, it is important to note that the dataset for ankle Doppler signals was only partially complete (83/97 patients). Where Doppler data were not recorded before treatment, this reflected the urgency with which patients presenting with severe acute ischemia were treated by heparinization, angiography, and/or surgery. Three (21.4%) of 14 patients who did not have admission Doppler pressures recorded subsequently underwent amputation, compared with 18 (21.7%) of 83 whose admission Doppler pressures were recorded, thus implying no obvious selection bias. The presence of one or more clinical signs as identified here was associated with an amputation risk of 25.9% (95% CI, 16.4%-35.4%).

Blood tests. Abnormal CK levels (P < .001) and neutrophilia (P = .011), but not abnormal urea (P = .259), creatinine (P = .354), or bicarbonate (P = .887), on admission were significantly associated with amputation. Linear regression analysis confirmed that, in either the amputation or no-amputation group or in the entire cohort, no significant linear relationship existed between the duration of symptoms and CK levels on admission (P = .623, .582, and .405 for the three models, respectively). These data are demonstrated in Fig 1. When data were restricted to patients with muscle tenderness, there was still no significant relationship (P = .549).

Predictive factors in major amputation. Table V shows the factors identified in this study to have a significant relationship with amputation. CK demonstrates by far the strongest statistical relationship. To address the issue of confounding variables, patients presenting with graft occlusion who underwent primary amputation, all of whom had increased CK on admission (n = 6), were removed from analysis. There was still a highly significant relationship between admission CK and amputation (χ^2 = 23.3; P < .001). If the patients undergoing primary amputation were excluded from the dataset, there was still a very strong relationship between increased CK and amputation (χ^2 = 10.897; P = .003). The presence of one or more significant

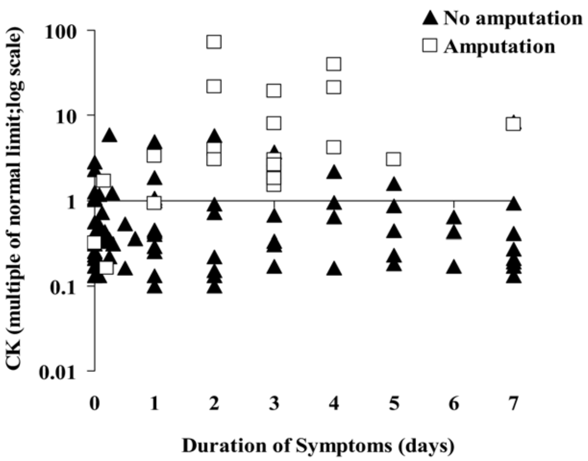

Fig 1. Scatterplot of creatine kinase *(CK)* levels on admission and amputation. Admission CK is plotted on a log scale according to the duration of acute symptoms. Linear regression analysis confirmed that, in either the amputation or no-amputation group or in the entire cohort, no significant linear relationship existed between the duration of symptoms and CK levels on admission (*P* = .623, .582, and .405 for the three models, respectively).

clinical signs, as shown in Tables III and V, was associated with an amputation risk of 25.9% (95% CI, 16.4%-35.4%), whereas increased CK implied a risk of 56.3% (95% CI, 39.1%-73.5%).

Predictive testing using CK. ROC curves were constructed for CK. This approach was not possible for the categorical prognostic factors. CK levels were expressed as a proportion of the upper limit of normal, because the normal ranges were different in men and women (200 and 150 U/L, respectively). Figure 2 shows that there was an exceptionally strong relationship between CK and amputation. The area under the curve for CK was 0.87 (95% CI, 0.78-0.97). These data show that a higher level of CK is associated with a higher risk of amputation.

Utility of CK as a clinical test. Having established that increased CK was associated with an increased occurrence of major amputation, positive predictive values were calculated by using a number of thresholds at which the test result was considered indicative of irretrievable ischemia. A range of empirical thresholds was chosen because there are no established levels. Figure 3 shows that the likelihood of the tests being correct (true-positive rate) in predicting major amputation increased from 56.3% (95% CI, 39.1%-73.5%), when the threshold corresponded to any result above the upper limit of normal (n = 34), to 100%, when CK was greater than 10 times the upper limit of normal (n = 5). Conversely, a normal CK result conferred a risk of major amputation of 4.6% (95% CI, 0.0%-9.7%; n = 63). These data show that the false-positive rate for CK greater than 10 times the upper limit of normal was 0, and the CI was also 0. Looking at only the patients who required surgery, the mean CK ($\log_{10}$ transformed to correct for asymmetry) in patients who did not require amputation was 0.47 times the upper limit of normal (95% CI, 0.35-0.63; n = 52), whereas the mean CK level for those who did was 3.92 times normal (95% CI, 2.07-7.43; n = 21).

DISCUSSION

This study aimed to identify symptoms, signs, and laboratory markers on admission that could provide an accurate prognosis in acute limb ischemia. Clinical signs, such as mottling, muscle tenderness, motor loss, sensory loss, and absent ankle Doppler signals were significantly associated with major amputation. However, none of these gave a positive predictive value greater than 50%. In contrast to the categorical nature of these clinical findings, CK levels offered the possibility of a continuous numerical index of amputation risk. The data showed that normal CK on admission was associated with a low risk of amputation (<5%), whereas increasingly abnormal CK was associated with an increasing risk of major amputation. Any increase in CK equated to a risk of greater than 50%, and 5 or 10 times normal conferred amputation risks of 70% and 100%, respectively. Plasma CK levels on admission may be a useful, simple, and rapid test to assist operative decision making in acute limb ischemia.

Studies that have addressed acute limb ischemia have suffered from the lack of a useful, internationally agreed definition.[6] Because chronic ischemia requires a duration of 2 weeks or more to establish the diagnosis,[7] some authors have opted to define acute ischemia in terms of new symptoms arising in a previously stable limb for less than 14 days.[8,9] Other groups have opted for a purely clinical definition.[2,10] Although there has been an attempt to standardize the accepted clinical features of acute limb ischemia,[11] this was not evidence based. In selecting a time frame for patients with acute ischemia for this study, 7 days was chosen. Other authors have reported that more severe ischemia is likely to present with a shorter history.[12] Previous studies in the Edinburgh Vascular Unit have shown that patients presenting as emergency cases with new symptoms of greater than 7 days' duration uniformly show normal CK levels on admission (Authors' unpublished observations, 2002). Presumably, evidence of muscle injury in those with shorter histories reflects the intense pain of truly severe, acute, limb ischemia, prompting patients to seek help more urgently.

Historical risk factors. Retrospective studies of acute limb ischemia have shown a number of significant associations with major amputation. A history of two or more myocardial infarctions, chronic limb ischemia, and symptoms lasting more than 25 hours were all significantly associated with limb loss within 30 days of an acute ischemic event.[1] The data shown here reveal that the only significant association with amputation in the medical history was previous vascular surgery, whereas the presence of peripheral vascular disease or the duration of symptoms did not confer significant added risk. In the amputation group, 9 of 21 had undergone previous vascular surgery, of whom 6 presented with graft occlusion, all with increased CK. Patients who have had previous bypass grafting with acute

Table V. Predictive factors for major amputation

Variable	*n (%)*	P *value*	*Amputation, n (%)*	χ^2	*Positive predictive value % (95% CI)*
Increased creatine kinase	32 (33.0)	<.001	18/32 (56.25)	33.7	56.3 (39.1-73.5)
Muscle tenderness	31 (32.0)	<.001	14/31 (45.2)	14.8	45.2 (27.7-62.7)
Vascular surgery	20 (20.6)	.012	9/20 (45)	8.1	45.0 (23.9-66.1)
Motor loss	31 (32.0)	.001	13/31 (41.9)	12.1	41.9 (24.5-59.3)
Mottling	38 (39.2)	.001	15/38 (39.5)	11.4	39.5 (24.0-55.0)
Sensory loss	51 (52.6)	.001	17/51 (33.3)	8.7	33.3 (20.4-46.2)
Neutrophilia	50 (51.5)	.011	16/50 (32)	6.5	32.0 (19.1-44.9)
Absent ankle Dopplers	57 (68.7)	.008	17/57 (29.8)	7.1	29.8 (17.9-41.7)

This table shows all the predictive factors identified from the history, examination, and simple investigations that were significantly associated with amputation. The number and percentage with each finding are shown, along with the associated P value, χ^2 statistic, and positive predictive value. The number of patients (%) demonstrating the abnormality who underwent amputation is also given. The statistical data relate to the association with major amputation.

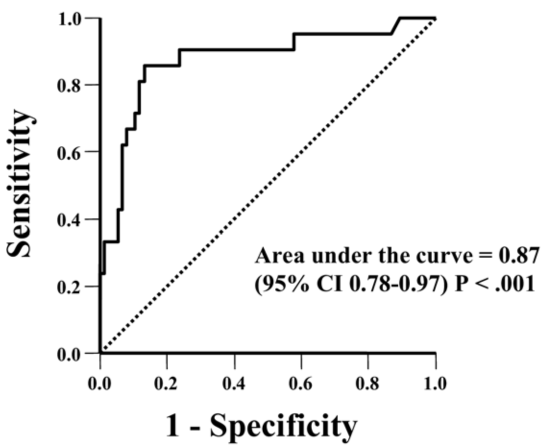

Fig 2. Receiver operator characteristic curve for plasma creatine kinase on admission as a test predictive of major amputation. The curve demonstrates that there is a very strong relationship between increased plasma creatine kinase (CK) and an increased risk of amputation ($P < .001$) and that the higher the plasma CK, the higher the amputation risk. Sensitivity is the true-positive rate, and 1 − specificity is the false-positive rate. *CI,* Confidence interval.

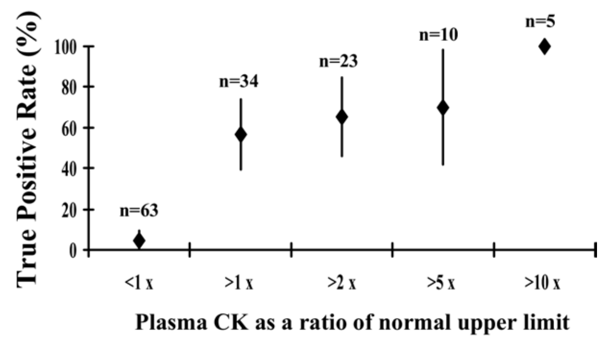

Fig 3. Creatine kinase *(CK)* levels as a predictive clinical test in acute limb ischemia. The data are shown as the true-positive rate (positive predictive value) with the associated 95% confidence intervals. The true-positive rate describes the percentage of positive test results, for example, CK above threshold, that are associated with amputation. Admission plasma CK was expressed as a multiple of the upper limit of normal CK for men (200 U/L) or women (150 U/L) and grouped into arbitrary subgroups, either below the upper limit of normal (<1×) or greater than once (>1×), twice (>2×), 5 times (>5×), or 10 times (>10×) the upper limit of normal. The number of patients in each group is shown. It should be noted that, for each subgroup, all applicable patients were included, and so any patient whose CK was greater than 10 times normal would qualify for inclusion in each of the lesser subgroups. The 95% confidence interval for CK >10× normal was 0, because all patients underwent amputation in this group.

occlusion often present with profound ischemia and few surgical options. It was therefore expected that a link between previous vascular surgery and amputation would be detected in this work. However, this raised the possibility that the observed relationship between CK and amputation may arise solely as a result of previous vascular surgery as a confounding variable. To address this issue, the statistical analysis was repeated after these six patients had been removed from the data set. This showed there was still a highly significant relationship between admission CK and amputation.

Clinical findings. Prospective investigations have demonstrated that specific clinical signs are strongly associated with failure of limb salvage. Neurologic dysfunction on admission or an absence of ankle Doppler signals halves 30-day limb-salvage rates in patients with acute limb ischemia,[2] although much of the salvage failure was attributable to mortality. That study is not strictly comparable with the present data, because patients with symptoms present for 6 weeks or less were chosen. Nonetheless, the present work confirms these observations. The data presented here also demonstrate a significant association between muscle tenderness/limb mottling and amputation. Both are indicators of more advanced ischemia compared with neurologic dysfunction or absent Doppler signals. In clinical practice, the diagnosis of acute severe limb ischemia in the presence of muscle tenderness and mottling is likely to present less prognostic difficulty than other, more subtle, signs. However, these signs are associated with amputation in only 40% to 45% of cases, and so even limbs that offer a "full house" of symptoms and signs may be remediable in more than half of all cases. The decision whether to transfer such a patient to a specialist vascular center for emergency revascularization or whether to recommend amputation within the originating hospital might be made easier if plasma CK levels were also available.

Laboratory studies. CK has previously been measured in three small series of patients with limb ischemia. A Swedish study of nine patients scheduled electively to undergo major lower limb amputation for chronic ischemia recorded CK levels of greater than twice normal in four of the group, of whom three had newly progressive symptoms at the time of sampling.[4] In a group of seven patients admitted as emergency cases with acute limb ischemia, the median preoperative CK was 367 U/L (range, 38-1149 U/L), compared with the upper limit of normal of 200 U/L.[13] No definition of acute ischemia was included in this article; however, the descriptions of each patient suggest an acute presentation for each. In this group of seven patients, two subsequently had major amputations, a proportion that generally agrees with the observations made in this study.

Surprisingly, the data presented here showed no relationship between the CK level and the duration of symptoms, even when the analysis was restricted to those with muscle tenderness. Presumably, ischemic muscle perfusion dynamically varies according to intravascular clot propagation and lysis, thus leading to varying symptoms and plasma CK levels. Observations in one patient who ultimately underwent amputation when stabilized showed that CK progressively increased after the onset of irretrievable ischemia. There may be an early phase of acute ischemia, during which the ischemic injury is dynamic and perhaps reversible, followed by a progressive and irreversible phase. Such a hypothesis would require further study.

In a series of patients who had undergone cardiac surgery, gross increases in CK were noted in some patients, and a relationship was observed with acute limb ischemia.[14] Twelve patients had clinical signs of acute limb ischemia, and the median CK level was 17,472 U/L in this group. By contrast, the median CK in the remaining patients was 7442 U/L, as compared with 135 U/L in patients undergoing routine elective cardiac surgery. These observations suggest that CK might be helpful in determining the presence of severe limb ischemia in sedated, ventilated, cardiac surgical patients. However, this study clearly set out to assess the significance of increased CK in cardiac surgical patients, rather than the significance of increased CK in patients with acute limb ischemia. Such findings in a highly specialized patient group should be extrapolated with caution to the general population with acute limb ischemia.

Other markers of muscle injury as indices of limb viability after acute ischemia have been investigated in experimental and clinical studies. In the rabbit, plasma taurine levels closely correlate with histologic and electron microscopic evidence of muscle cell death after acute severe ischemia.[15] Conversely, muscle adenosine triphosphate or lactate content, but not serum myoglobin or carbonic anhydrase, was strongly predictive of the need for amputation in patients.[16] These tests, which involve chemical extraction of tissue specimens, are less practical and much more time consuming than the ubiquitous CK estimation.

If CK had been used to inform clinical decision making in this study, it is possible that the secondary amputation rate (38.1%) would have been reduced. Five patients who underwent secondary amputation had increased CK on admission. In all five cases, the consultant surgeon had thought the limbs potentially salvageable. The CK test strongly suggested that limb loss was overwhelmingly likely in two patients and more likely than not in the remaining three. It is noteworthy that these patients formed a substantial subgroup (24%) of those undergoing amputation. If CK greater than 10 times normal was taken as the threshold for irreversible ischemia, then at least two patients undergoing amputation as a secondary procedure would have been prepared for primary amputation alone.

Neutrophilia—but not urea, creatinine, or bicarbonate levels—was significantly associated with amputation. Patients with acute limb ischemia often present with acute comorbidities, such as chest infection or urinary tract infection. Such infections can precipitate an acute thrombophilia due to dehydration and activation of inflammatory and coagulation cascade mediators and so be a causal factor in limb ischemia. It was believed that neutrophilia may be confounded by coexistent disease in limb ischemia and could not be relied upon as a prognostic marker. With regard to markers of renal dysfunction, other authors have shown no relation between creatinine and amputation in a large retrospective assessment from Sweden.[1]

In conclusion, this study set out to investigate markers of irreversible tissue injury in emergency admissions with acute lower limb ischemia and to assess whether any might be useful prognostic indicators of limb salvage or major amputation. The results showed that a history of vascular surgery, specific clinical signs of ischemia, and increased CK on admission were significantly associated with major amputation. Whereas none of the clinical indicators of ischemia had a positive predictive value greater than 50%, increased CK immediately suggested that amputation was more likely than limb salvage, whereas normal CK virtually ensured limb salvage unless secondary events ensued. Larger multicenter studies of CK in acute limb ischemia are warranted to further explore this very strong relationship. The widespread availability of CK estimations and the objective nature of this test may significantly extend the prognostic tools available to specialists and nonspecialists alike who manage acute limb ischemia.

AUTHOR CONTRIBUTIONS

Conception and design: ISC, RTC
Analysis and interpretation: ISC, AJL
Data collection: ISC, SJW
Writing the article: ISC
Critical revision of the article: ISC, SJW, AJL, RTC
Final approval of the article: ISC, SJW, AJL, RTC
Statistical analysis: ISC, AJL
Overall responsibility: ISC, RTC

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Submitted Aug 24, 2006; accepted Dec 15, 2006.