Prognostic factors for amputation or death in patients submitted to vascular surgery for acute limb ischemia

Clebes Fagundes[1]
Flávio Danni Fuchs[2]
Almondi Fagundes[1]
Ronaldo A Poerschke[1]
Maurício Z Vacaro[1]

[1]Divisions of Vascular Surgery, Hospital São Vicente de Paulo, Faculdade de Medicina da Universidade de Passo Fundo; [2]Cardiology, Hospital de Clínicas de Porto Alegre, Faculdade de Medicina da Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

Objective: To investigate the risk profile of patients with thrombosis and emboli, and prognostic factors for death or amputation in patients presenting with acute limb ischemia in a tertiary care regional hospital in Brazil.

Methods: A prospectively planned cohort study was carried out in which 83 patients with acute limb ischemia, secondary to thrombosis, or embolism, classified in stages II and III of severity were evaluated. Univariate analysis and logistic regression models were used to explore the relationship between anthropometric and demographic characteristics, comorbidities, cardiovascular risk factors, duration of occlusion, and type of surgery with the incidence of amputation or death, which were evaluated in 30 days and 1 year thereafter.

Results: Male gender, smoking, and comorbidities were more frequent among patients with thrombosis, and atrial fibrillation was more common among patients with embolism. Occlusion longer than 24 hours (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.1–7.6) and a trend for diabetes (RR 2.6, 95% CI 0.9–7.5) were the characteristics associated with death or amputation in the multivariate analysis, which occurred in 15 (18.1%) and 24 (28.9%) of the participants, respectively. Reperfusion injury was a risk factor for death but not for amputation (OR 16.9, 95% CI 1.1–232.9) after adjustment for age, duration of occlusion, and diabetes.

Conclusions: Traditional and avoidable risk factors explain the occurrence of thrombosis and embolism in our region. Access to medical care is the most important and modifiable prognostic factor for death or amputation.

Keywords: acute limb ischemia, embolism, thrombosis, prognostic factors

Introduction

Cardiovascular disease is the leading cause of death in Brazil (Mansur et al 2001). Acute limb ischemia is responsible for a high proportion of morbidity and mortality attributable to cardiovascular disease. It is caused by thrombosis or embolism from the heart or major arterial branches (Haimovici 1982; Perry 1995; Murabito et al 1997). Surgical revascularization or endovascular therapy is a major determinant of not only limb but also life survival in such a population of patients (Hertzer 1991). The results of the surgical revascularization by thromboembolectomy or bypass may be influenced by several prognostic factors: eg, antecedent cardiovascular risk factors, duration and presentation of the acute episode, surgical technique, and location of occlusion, to mention a few (Perry 1995; Rutherford et al 1997; TASC 2000). The identification of different prognostic factors may reflect the experience of different centers, but may be also biased by confounding factors. Prognosis of patients with embolism was previously described (Aune and Trippestad 1998), but we are not aware of any study of prognostic factors in patients with acute limb ischemia secondary

Correspondence: Flávio Danni Fuchs
Serviço de Cardiologia, Hospital de Clínicas de Porto Alegre, Ramiro Barcelos, 2350, 90035-003, Porto Alegre, RS, Brazil
Tel +55 51 2101 8420
Fax +55 51 2101 8420
Email ffuchs@hcpa.ufrgs.br

to thrombosis or embolism treated surgically in our country. In this study, we compared the risk profile of patients with thrombosis and embolism, and investigated prognostic factors for death or amputation in patients with acute limb ischemia classified in stages II and III of severity (Rutherford et al 1997).

Methods

A prospectively planned cohort study was carried out in a tertiary care regional hospital through a prospective registry format. Patients were referred from provincial hospitals or were seeking assistance directly in our hospital. The comprising cohort of patients was from a region with approximately one million inhabitants. All patients with acute limb ischemia, secondary to thrombosis, embolism, or trauma, were screened. Acute limb ischemia was characterized as a quick or sudden decrease in limb perfusion, producing new or worsening symptoms, and signs of threatening limb viability. Patients with embolism or thrombosis in categories II and III of severity, and submitted to surgical revascularization or primary amputation, were enrolled in the study. The categories of acute limb ischemia were classified according to the protocol of Rutherford et al (1997).

The protocol included assessment of anthropometric and demographic data, comorbidities and risk factors, duration of occlusion, and type of surgery. Hypertension, hypercholesterolemia, and diabetes were characterized by history or use of blood pressure-lowering drugs, hypolipemiant, or antidiabetic drugs. Past (time of quitting not specified) and current smokers were classified as smokers. Coronary heart disease was diagnosed in the presence of a history of a previous myocardial infarction, angina or a "Q" wave in the electrocardiogram. Atrial fibrillation was diagnosed by an electrocardiogram taken during the acute vascular episode. The diagnosis of stroke was based on history or evidence of motor deficit. Previous peripheral artery disease was characterized by history of intermittent claudication. Renal insufficiency was defined by creatinine over 3.0 mg per deciliter or hemodialysis. Duration of occlusion was estimated by the time between the onset symptoms of acute limb ischemia (first symptoms) and the arrival in the emergency room of our hospital. The American Society of Anesthesiologists (ASA) risk category was used by the anesthesiologist for the purpose of classification.

Six vascular surgeons, all with 3–5 years of training in medical residency, and with at least 5 years of experience, performed all surgeries.

The primary outcome was the occurrence of death or amputation in 30 days and 1 year. These events were analyzed separately as secondary outcomes. The occurrence of death or amputation by several prognostic characteristics was tested by the Chi square test. Student's t-test was employed to test for differences in continuous variables between patients with thrombosis and embolism. Logistic regression models were used to explore the relationship between prognostic factors for amputation or death in 30 days. A Cox proportional hazard model was used to explore these associations during the follow-up of 1-year, including time-to-event as covariate.

The study was approved by the Ethical Committee of our Institution. We ensured the anonymous identification of the participants.

Results

In total, 83 sequential patients with acute limb ischemia classified in the Rutherford categories II and III (16 in category III) of severity, were enrolled between 1997 and 2000. The cohort was followed for 1 month and 3 were lost after this period in the follow-up to one year. The main cause of limb ischemia in this cohort was thrombosis (56.6%) with the remaining cause being due to emboli (43.4%). The demographics of patients studied are presented in Table 1. It is evident that patients with thrombosis were more frequently male and smokers. Comorbidities were also more frequent among patients with thrombosis, with the exception of atrial fibrillation, which was more common among patients with embolism. Only 1 patient with embolism

Table 1 Demographics of population of patients with limb ischemia that were studied (mean ± SD or n (%) within stratum)

Characteristics	Embolism (n = 36)	Thrombosis (n = 47)	P
Age (y)	67 ± 12	69 ± 10	NS
Male gender	12 (33.3)	36 (76.6)	< 0.001
Previous vascular procedure	9 (25)	13 (27.7)	NS
Duration of occlusion (h)	38 ± 79	41 ± 46	NS
Smoking	10 (27.8)	40 (85.1)	< 0.001
Diabetes mellitus	7 (19.4)	20 (42.6)	0.034
Hypertension	15 (41.7)	17 (36.2)	NS
Coronary artery disease	14 (38.9)	22 (46.8)	NS
Cerebral vascular disease	0	7 (14.9)	0.017
Peripheral vascular disease	6 (16.7)	35 (74.5)	< 0.001
Hyperlipidemia	7 (19.4)	1 (2.1)	0.019
Atrial fibrillation	20 (55.6)	11 (23.4)	0.003
Renal insufficiency	1 (2.8)	1 (2.1)	NS
ASA	2.89 ± 0.46	2.83 ± 0.67	NS

Abbreviations: ASA, American Society of Anesthesiologists classification; h, hours; y, years.

Table 2 Level of occlusion in participants classified by the cause of limb ischemia (n and %)

Site	Embolism (n = 36)	Thrombosis (n = 47)
Infrarenal aorta	2 (5.6)	6 (12.8)
Common iliac	3 (8.3)	3 (6.4)
External iliac	4 (11.1)	8 (17.0)
Common femoral	6 (16.7)	1 (2.1)
Superficial femoral	14 (38.8)	19 (40.4)
Popliteal above-knee	5 (13.9)	6 (12.8)
Popliteal below-knee	0	4 (8.5)
Posterior tibial	2 (5.6)	0

and 2 with thrombosis were submitted to duplex scanning. Angiography was done in 5 (13.9%) of the patients with embolism and in 23 (48.9%) of the patients with thrombosis (p < 0.001). Fasciotomy was done in 6 (16.7%) of the patients with embolism and in 1 (2.1%) of the patients with thrombosis (p = 0.039). The level of occlusion is presented in Table 2 and the surgical procedures employed in the management of these cases are presented in Table 3. Occlusion at the level of superficial femoral artery accounted for almost 50% of the cases of embolism and thrombosis. In patients with embolism, the common femoral artery was the second site of occlusion, while in patients with thrombosis the external iliac artery was the second site of occlusion. Almost all patients with embolism were treated by thromboembolectomy, while the cases of thrombosis were managed with bypass using venous and artificial grafts and endarterectomy. Endovascular therapy and thrombolysis were not in use at the time of data collection. Only patients with thrombosis were submitted to primary amputation (19.1%).

There were 15 (18.1%) deaths and 24 (28.9%) amputations in the cohort of patients investigated. The incidence of amputation or death according to the presence of prognostic factors is presented in Table 4. Duration of

Table 3 Type of surgical procedures to deal with limb ischemia (n and %)

Procedure	Embolism (n = 36)	Thrombosis (n = 47)
Thromboembolectomy	35 (97.2)	1 (2.1)
Bypass in situ GSV		10 (21.3)
Bypass reversed GSV		6 (12.8)
Bypass PTFE or Dacron	1 (2.8)	13 (27.7)
Primary amputation		9 (19.1)
Endarterectomy		7 (14.9)
Composite bypass		1 (2.1)

Abbreviations: GSV, greater saphenous vein; PTFE, polytetrafluoroethylene.

Table 4 Incidence of amputation or death by baseline characteristics, duration of surgery, or cause of occlusion (n and %)

Characteristics	Condition (n)	Amputation or death	p
Gender	Female (35)	20 (57.1)	0.376
	Male (48)	22 (45.8)	
Age (y)	< 65 (33)	15 (45.5)	0.505
	> 65 (50)	27 (54.0)	
Cause of occlusion	Thrombosis (47)	24 (51.1)	1.0
	Embolism (36)	18 (50.5)	
Atrial fibrillation	Yes (31)	16 (51.6)	1.0
	No (52)	26 (50.0)	
Cerebral vascular disease	Yes (7)	4 (57.1)	1.0
	No (76)	38 (50.0)	
Coronary artery disease	Yes (36)	21 (58.3)	0.270
	No (47)	21 (44.7)	
Diabetes mellitus	Yes (27)	18 (66.7)	0.061
	No (56)	24 (42.9)	
Smoking	Yes (50)	23 (46.0)	0.372
	No (33)	19 (57.6)	
Duration of occlusion (h)	> 24 (42)	26 (63.4)	0.028
	< 24 (41)	16 (38.1)	
Hypertension	Yes (32)	17 (53.1)	0.822
	No (51)	25 (49.0)	
Hyperlipidemia	Yes (8)	3 (37.5)	0.717
	No (75)	39 (52.0)	
Peripheral vascular disease	Yes (41)	21 (51.2)	1.0
	No (42)	21 (50.0)	
Angiography	Yes (28)	11 (39.3)	0.168
	No (55)	31 (56.4)	
Level of occlusion	Proximal (33)	16 (48.5)	0.824
	Distal (50)	26 (52.0)	

Abbreviations: h, hours; y, years.

occlusion was one characteristic associated with a poor prognosis while the presence of diabetes showed a trend for poor prognosis. These associations persisted in a logistic regression model that included themselves with age, gender, hypertension, and cause of occlusion as explanatory variables (Table 5). The same trends persisted during the follow-up of one year, adjusting for the same set of confounding variables. The hazard ratio for death or amputation for duration of occlusion longer than 24 hours was 1.7 (95% confidence interval [CI] 0.9–3.3). For diabetes the hazard ratio was 1.6 (95% CI 0.8–2.9). Three cases were censored at 1-month of follow-up.

In the logistic regression models that included death and amputation separately as dependent variables, the odds ratios (OR) were among the 95% confidence estimates of the composite endpoint, and presented a similar trend for risk

Table 5 Prognostic factors for death or amputation in 30 days as analyzed by logistic regression model

Characteristics	OR (95% Confidence interval)	p
Female gender	1.4 (0.5–4.3)	0.39
Age > 65 (y)	1.4 (0.5–3.8)	0.53
Duration of occlusion > 24 (h)	2.6 (1.1–7.6)	0.03
Diabetes	2.6 (0.9–7.5)	0.07
Hypertension	0.9 (0.4–2.5)	0.92
Embolism*	1.4 (0.4–4.4)	0.58

Abbreviations: h, hours; OR, odds ratio; y, years.
NOTE: Adjusted for age, gender, duration of occlusion, diabetes, and cause of occlusion.
* The control group was constituted by patients with thrombosis.

or protection. Hypertension showed a trend for protection against amputation (OR 0.3, CI 0.1–1.1 p = 0.06) but was associated with the risk of death (OR 3.7, CI 1.2–11.5, p = 0.03).

The level of occlusion, stratified in proximal (aorta, common iliac, external iliac, and common femoral artery) and distal (superficial femoral, popliteal, anterior and posterior tibial, and peroneal artery), was not associated with the incidence of death, amputation, or both.

The incidence of reperfusion injury (limb swelling with impaired muscle function with or without systemic manifestations) due to ischemia was 6.0%, being restricted to patients with embolism (13.9%). It was a risk factor for death, but not for amputation in these patients (OR 16.9, 95% CI 1.1–232.9, p = 0.04) after adjustment for age, duration of occlusion, and diabetes.

Discussion

Thrombosis was more frequent than embolism as a cause of nontraumatic limb ischemia in our hospital. A higher proportion of embolism (Aune and Trippestad 1998), thrombosis (Ouriel and Veith 1998), and a similar frequency of both conditions (Gutowski et al 1999) have been described. Patients with thrombosis were more frequently male and had higher prevalence of cardiovascular risk factors and comorbidities, such as a previous diagnosis of peripheral vascular disease and cerebrovascular disease. As expected, patients with embolism more often had atrial fibrillation (Brewster 1995).

The incidence of death or amputation was almost 50% as described in other centers (Balas et al 1985; Littoy and Baker 1986; Varty et al 1992; Braithwaite et al 1998). The independent risk factor for an unfavorable outcome was prolonged time between the beginning of symptoms and the surgery. Diabetes also showed a trend for such risk (ie,

unfavorable outcome). These prognostic factors have been previously described (Balas et al 1985; VSSGBI 1995; TASC 2000). In the Basle study, it was reported that major amputations were 11 times more frequent in diabetic patients with peripheral arterial disease (PAD) than in nondiabetic PAD patients (Da Silva et al 1979). Duration of occlusion was the most important modifiable cause of amputation or death in our cohort. We did not analyze specific causes for the long interval between the beginning of symptoms and the arrival at the emergency department. We speculate that the low level of education of most patients, their fear of doctors, and misdiagnosis may be underlying causes for such catastrophic behavior.

Hypertension showed a trend for protection against amputation but was significantly associated with a higher risk of death. Although Jelnes et al (1986) noted that the risk of deterioration was related to blood pressure, the study by Dormandy and Murray (1991) did not find a significant link between hypertension and prognosis after adjustment for other risk factors. Our findings may be ascribed to chance, but the possibility that higher blood pressure during such events protects against the failure of grafts needs to be further investigated in a systematic manner.

Cigarette smoking is a major risk for developing peripheral arterial disease (Kannel and Shurtleff 1973; Da Silva et al 1979), but we could not find any association between smoking that influenced the prognosis of acute limb ischemia. This risk factor deserves further investigation since our negative findings could be attributed to sample size and a lower statistical power of our study.

The incidence of reperfusion injury was restricted to patients with embolism and was a risk factor for death. This has been well recognized as a serious complication of revascularization (TASC 2000).

In conclusion, acute limb ischemia caused by thrombosis or embolia was identified as a serious medical event in our hospital, being associated with high rates of mortality or amputation. In general, atherosclerotic vascular disease was a risk factor for thrombosis, while atrial fibrillation was a strong risk factor for embolism. It seems that the time interval for medical care and attention is one of the most important and modifiable prognostic factors for either death or amputation.

References

Aune S, Trippestad A. 1998. Operative mortality and long-term survival of patients operated on for acute lower limb ischaemia. *Eur J Vasc Endovasc Surg*, 15:143–6.

Balas P, Bonatsos G, Xeromeritis N, et al. 1985. Early surgical results on acute arterial occlusion of the extremities. *J Cardiovasc Surg*, 26:262–9.

Braithwaite BD, Davies B, Birch PA, et al. 1998. Management of acute leg ischaemia in the elderly. *Br J Surg*, 85:217–20.

Brewster DC. 1995. Arterial tromboembolism. In Rutherford RB (ed). Vascular surgery. 4th ed. Philadelphia: WB Saunders. p 647–66.

Da Silva A, Widmer LK, Ziegler HW, et al. 1979. The Basle longitudinal study; report on the relation of initial glucose level to baseline ECG abnormalities, peripheral artery disease, and subsequent mortality. *J Chron Dis*, 32:797–803.

Dormandy J, Heeck L, Vig S. 1999. Acute limb ischemia. *Semin Vasc Surg*, 12:148–53.

Dormandy JA, Murray GD. 1991. The fate of the claudicant: a prospective study of 1969 claudicants. *Eur J Vasc Surg*, 5:131–3.

Gutowski P, Soltys J, Rac M, et al. 1999. The treatment of acute lower limb ischemia. *Wiad Lek*, 52:252–6.

Haimovici H. 1982. Acute atherosclerotic thrombosis. In Haimovici H (ed). Vascular emergencies. New York: Appleton-century–crofts. p 213–22.

Hertzer NR. 1991. The natural history of peripheral vascular disease. Implications for its management. *Circulation*, 83(2 Suppl):I12–19.

Jelnes R, Gaardsting O, Hougaard Jensen K, et al. 1986. Fate in intermittent claudication: outcome and risk factors. *Br Med J*, 293:1137–40.

Kannel WB, Shurtleff D. 1973. The Framingham Study. Cigarettes and the development of intermittent claudication. *Geriatrics*, 28:61–8.

Littoy FN, Baker WH. 1986. Acute aortic occlusion – a multifaceted catastrophe. *J Vasc Surg*, 4:211–16.

Mansur AP, Favarato D, Souza MF, et al. 2001. Trends in death from circulatory diseases in Brazil between 1979 and 1996. *Arq Bras Cardiol*, 76:504–10.

Murabito JM, D'Agostino RB, Silbershatz H, et al. 1997. Intermittent claudication. A risk profile from the Framingham Heart Study. *Circulation*, 96:44–9.

Ouriel K, Veith FJ. Acute lower limb ischemia: determinants of outcome. *Surgery*, 1998; 124:336–41

Perry MO. 1995. Acute arterial insufficiency. In Rutherford RB (ed). Vascular surgery. 4th ed. Philadelphia: WB Saunders. p 641–6.

Rutherford RB, Baker JD, Ernst C, et al. 1997. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*, 26:517–38.

[TASC] Transatlantic Inter-Society Consensus. 2000. Management of peripheral arterial disease (PAD). *J Vasc Surg*, 31:135–67.

Varty K, St Johnston JA, Beets G. 1992. Arterial embolectomy. A long-term perspective. *J Cardiovasc Surg*, 33:79–84.

[VSSGBI] Vascular Surgical Society of Great Britain and Ireland. 1995. Critical limb ischaemia: management and outcome. Report of national survey. *Eur J Vasc Endovasc Surg*, 10:108–13.