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CRITICIAL LIMB ISCHEMIA: EPIDEMIOLOGY

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Abstract

Critical limb ischemia is found in 12% of the U.S. adult population. Its clinical presentation varies from no symptoms to intermittent claudication, atypical leg pain, rest pain, ischemic ulcers, or gangrene. Those with critical limb ischemia have a high incidence of cardiovascular comorbidities that reflect a significant systemic atherosclerotic burden; they have increased functional impairment and increased rates of functional decline compared with persons without critical limb ischemia. Interventions for critical limb ischemia and the impact of major amputation have a significant social and economic impact. At 1 year, 25% of patients will be dead, 30% will have undergone amputation, and only 45% will remain alive with both limbs. At 5 years, more than 60% of patients with critical limb ischemia will be dead.

Introduction

Eight to ten million Americans suffer from arterial occlusive disease, leading to approximately 500–1,000 new cases of chronic limb ischemia per million people per year.[1] The prevalence of critical limb ischemia is 12% in the adult population, with men affected slightly more than women. This prevalence is age-dependent as well, with nearly 20% of adults age 70 and older carrying a diagnosis of critical limb ischemia. As the population ages, the impact of this disease on health care will be magnified. The PARTNERS (PAD Awareness, Risk, and Treatment: New Resources for Survival) study found critical limb ischemia present in 29% of the study patients aged 70 years and older and aged 50 to 69 years with at least a 10-pack-per-year history of smoking or a history of diabetes.[2] Greater than 70% of primary care providers in the PARTNERS study were unaware of the presence of critical limb ischemia in their patients who had the disease. Coexistent coronary artery disease (CAD) and cerebrovascular disease (CVD) are highly prevalent (63%) in patients with critical limb ischemia, particularly in the elderly population. Patients over the age of 50 with critical limb ischemia in an academic, hospital-based geriatric practice have a 68% and 42% incidence of coexistent CAD and stroke, respectively.[3] The Reduction of Atherothrombosis for Continued Health (REACH) registry showed that one of six patients with peripheral arterial disease (PAD), CVD, or CAD had involvement of one or two other arterial beds.[4, 5] The REACH registry also demonstrated a substantial gap between recommended clinical guidelines and actual clinical practices in caring for patients with or at risk for atherothrombosis. A pattern of underutilization of established medical therapies and lifestyle interventions was shown throughout all geographic regions studied and vascular disease subtypes.[4]

Chronic limb ischemia reflects the local manifestations of a lethal systemic disease — atherosclerosis. If left untreated, chronic limb ischemia can result in major limb loss. Critical limb ischemia can be separated into four distinct cohorts: asymptomatic, claudication, critical limb ischemia with rest pain, and critical limb ischemia with tissue loss. The natural history of critical limb ischemia is well documented. At 1 year, 25% of patients will be dead, 30% will have undergone amputation, and 45% will be alive with both limbs.[1] More than 60% of patients with critical limb ischemia will be dead at 5 years.[6] Patients with critical limb ischemia are at an exceptionally high risk for cardiovascular events, and the majority will eventually die of a cardiac or cerebrovascular event. The more symptomatic and severe the critical limb ischemia as objectively measured by the ankle-brachial index (ABI), the worse the overall patient prognosis (Figure 1). In the REACH registry, the relative risk of dying among patients with large-vessel critical limb ischemia versus none was 3.1 (95% CI 1.9–4.9) for deaths from all causes and 5.9 (95% CI 3.0–11.4) for all deaths from cardiovascular disease. Mortality due to cardiovascular disease was 15-fold higher among symptomatic subjects with severe large-vessel critical limb ischemia. Finally, critical limb ischemia has been classified as a coronary heart disease (CHD) risk equivalent (i.e., carrying >20% risk of a coronary event in 10 years).

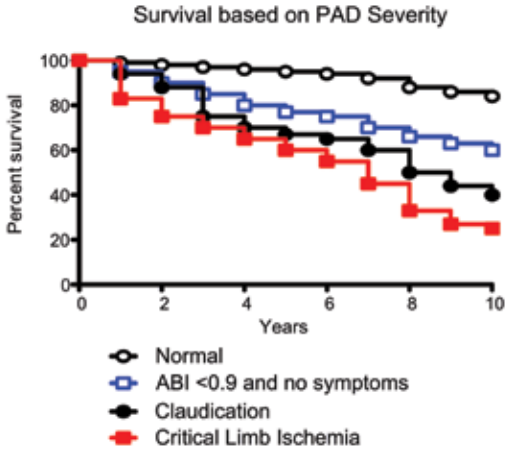

Figure 1. 10-year survival in patients with asymptomatic and symptomatic peripheral arterial disease.

The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001)[7] classified diabetes, multiple cardiac risk factors, and critical limb ischemia, including carotid disease and abdominal aortic aneurysm, as a CHD risk equivalent. The epidemic of diabetes and metabolic syndrome has escalated the number of lower-extremity problems presenting

for treatment. It has been estimated that 50% of diabetic patients have evidence of chronic critical limb ischemia.[8] Diabetics suffer from both micro- and macro-vascular disease of complex etiology, manifested often as ischemia but more frequently as motor or sensory neuropathies.[9] Globally, diabetes accounts for 1 amputation every 30 seconds and 80,000 amputations annually in the United States alone. Fifty percent of these patients will have an above- or below-knee amputation, 50% will require a second amputation within 5 years, and 50% will be dead in five years. Of those patients presenting with critical limb ischemia, 67% undergo a primary amputation, and 50% of these are performed without imaging or noninvasive testing. Of these amputations, 85% are considered preventable.[7]

Clinical Presentation and Diagnosis

The clinical presentation of critical limb ischemia may vary from no symptoms to intermittent claudication, atypical leg pain, rest pain, ischemic ulcers, or gangrene. The ABI is a simple test that can be conducted in the office and typically confirm the presence of disease. It is calculated by dividing the ankle pressure by the highest brachial pressure. An ABI <0.9 is abnormal and indicates critical limb ischemia. An ABI between 0.7 and 0.9 is considered mild disease, between 0.3 and 0.69 is moderate disease, and less than 0.3 is severe disease. There are many classifications for claudication and limb ischemia, but the most utilized is the Rutherford-Becker classification. Rutherford Grade I indicates essentially asymptomatic patients or symptoms during a very high level of activity; Rutherford Grade II is symptoms during a moderate level of activity; and Rutherford Grade III is symptoms during a low level of activity. Claudicants are considered to fall within Rutherford Grade I-III. Rutherford Grade IV is symptoms during rest and is termed "Rest Pain." Rutherford Grade V is forefoot ulceration, and Rutherford Grade VI is ulceration with tissue necrosis. Rutherford Grade V and VI are termed "Tissue Loss."

Claudication is the typical symptomatic expression of critical limb ischemia. However, asymptomatic disease may occur in up to 50% of these patients. Of the 460 patients with critical limb ischemia in the Walking and Leg Circulation Study,[10] 19.8% had no exertional leg pain, 28.5% had atypical leg pain, 32.6% had classic intermittent claudication, and 19.1% had pain at rest. The results of these and other studies indicate that more patients with critical limb ischemia are asymptomatic or have atypical leg symptoms than have classic intermittent claudication.

The presence of critical limb ischemia has two major consequences. The first is a decrease in overall well-being and quality of life due to reduced blood flow and atypical leg pain. This often leads to patients becoming sedentary due to pain and discomfort. They may develop depression. The second consequence is markedly increased cardiovascular morbidity (myocardial infarction and stroke) and mortality (cardiovascular and all-cause).

Risk Factors

Critical limb ischemia is most often diagnosed by an ABI ≤ 0.9. A low ABI is an independent predictor of increased mortality. In the Framingham Study, mortality in patients with intermittent claudication was 2–3 times higher than in age- and sex-matched control patients, with 75% of critical limb ischemia patients dying from cardiovascular events. In a 15-year review of patients with claudication, over 66% of mortality was attributable to CVD. In a 10-year prospective study by Criqui et al.,[11] critical limb ischemia patients both with and without a history of CVD had a significantly increased risk of dying from cardiovascular and coronary heart disease compared with age-matched control

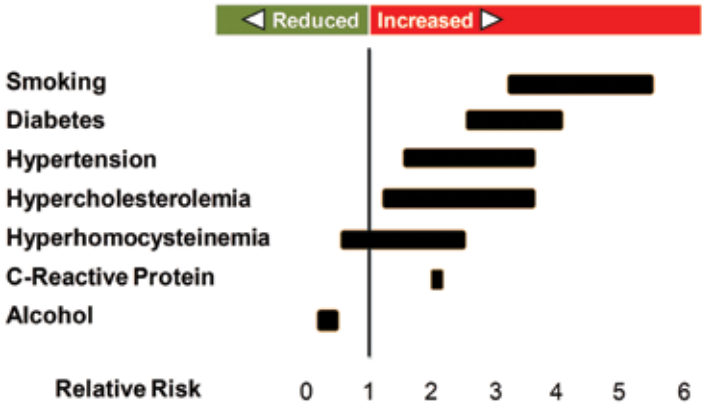

Figure 2. The relative importance of key risk factors in the progression of peripheral arterial disease.

patients. The all-cause mortality was 3.1 times greater and CVD mortality was 5.9 times greater in patients with critical limb ischemia compared to patients without critical limb ischemia. Studies have shown that the risk of cardiovascular events is similar between critical limb ischemia patients with claudication and those without symptoms. The extremely high morbidity and mortality in the critical limb ischemia population is due to myocardial infarction and stroke. Both the Edinburgh Artery Study[12] and the ARIC (Atherosclerosis Risk in Communities)[13] study correlated an increased risk of stroke and transient ischemic attack with increased severity of critical limb ischemia. The combination of known coronary or cerebrovascular disease and critical limb ischemia has been shown to increase mortality risk. The BARI (Bypass Angioplasty Revascularization Investigation) trial demonstrated that patients with multivessel CAD and critical limb ischemia had a relative risk of death 4.9-times greater than those without critical limb ischemia.[14, 15] Additionally, in a pooled analysis of eight randomized prospective trials involving 19,867 patients undergoing percutaneous coronary intervention, the 1-year mortality was 5% in patients with critical limb ischemia and coronary disease compared with 2.1% in patients with coronary disease alone ($p < 0.001$).[16]

Chronic limb ischemia is strongly associated with cardiovascular risk factors such as cigarette smoking, diabetes mellitus, dyslipidemia, hypertension, and hyperhomocysteinemia (Figure 2).[17-19] Cigarette smoking is associated with a marked increased risk for peripheral atherosclerosis, and 70–90% of patients with chronic limb ischemia are either current or ex-smokers.[17, 20-22] Follow-up of smokers and ex-smokers at 7 years shows that critical limb ischemia had developed in 16% of smokers but not in ex-smokers.[23] The 10-year incidence of myocardial infarction is five times greater in the smoking group compared to ex-smokers (53% vs. 11%). At 10-year follow-up, cardiovascular-related mortality in the smoking group is more than 50%, three times that of the nonsmoking group.

Elevated cholesterol has been shown in the Framingham study to be a weak but significant increased risk for chronic limb ischemia.[20] Lipid profile abnormalities, such as elevated serum triglyceride levels and reduced high-density lipoproteins, have been found in the majority of studies of patients with chronic limb ischemia,[24] and there is a strong inverse relationship between high-density lipoprotein levels and chronic limb ischemia severity.[25] Lipoprotein (a) levels have been shown to correlate with LDL, cholesterol fibrinogen levels, and with the severity of critical limb ischemia.[26] The Scandinavian Simvastatin Survival Study

(4S) demonstrated that subjects randomized to simvastatin had a 38% reduction in new or worsening claudication compared with subjects randomized to placebo.[27] Another study has demonstrated improved walking ability in patients treated with a statin compared to those not on a statin.[28]

Markers of inflammation have been associated with the development of atherosclerosis and cardiovascular events.[29,30] In particular, C-reactive protein (CRP) is independently associated with critical limb ischemia, even in patients with normal lipid levels.[31, 32] Higher CRP levels are associated with poorer functioning measures.[33] In the Physicians Health Study, an elevated CRP level was a risk factor for developing symptomatic critical limb ischemia as well as for peripheral revascularization.[34] Elevated plasma homocysteine levels are an independent risk factor for critical limb ischemia.[35-37] Although B-vitamin supplements can lower homocysteine levels, there is minimal evidence that they can help prevent cardiovascular events.[38, 39]

Platelets and their products are known to play a key role in atherosclerosis. Platelet activity has been shown to be 30% higher in patients with peripheral vascular disease even if they are asymptomatic.[40, 41] Not surprisingly, antiplatelet therapy has shown significant reductions in fatal and non-fatal vascular events in 'high-risk' vascular patients, e.g., claudicants.[42-44] The risk reduction for antiplatelet therapy versus placebo in the claudicant population was 46% for nonfatal stroke, 32% for nonfatal myocardial infarction, and 20% for death from a vascular cause. Even "low-risk" patients on antiplatelet therapy have shown small but significant risk reduction. Progression of peripheral atherosclerosis, as measured by angiography, has also been shown to be inhibited in antiplatelet-treated patients.[45] A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) had a large subgroup of patients with atherosclerotic vascular disease.[46] Clopidogrel was shown to have a small but significantly greater reduction in vascular morbidity and mortality than aspirin, and there were no major differences in safety profiles between the two drugs. Despite clopidogrel therapy, patients undergoing percutaneous coronary intervention with stenting are at risk of recurrent coronary events. This could be partly explained by a reduced efficacy of clopidogrel to inhibit platelet aggregation, an ex vivo-defined phenomenon called clopidogrel nonresponsiveness or resistance. Laboratory clopidogrel nonresponsiveness can be found in approximately 1 in 5 patients. It is inversely correlated with time between clopidogrel loading and determination of nonresponsiveness and loading dose used.[47]

Hemostatic abnormalities are found frequently in critical limb ischemia and may contribute to pathogenesis or be a marker of disease progression.[48-50] The presence of the lupus anticoagulant and elevated markers of platelet activation (beta thromboglobulin levels) have been associated with peripheral atherosclerosis.[51, 52] In a study by Gosk-Bierska et al., hemostatic abnormalities were present in diabetic subjects, with greater evidence of thrombin generation than in non-diabetics.[53] Clinical studies on patients undergoing peripheral bypass surgery have demonstrated the presence of a definite subset of patients with abnormal coagulation profiles.[54] After adjusting for age and sex, von Willebrand Factor (vWF), fibrin, D-dimer and urinary fibrinopeptide A are elevated in patients with critical limb ischemia, and the risk for claudication is significantly raised with unit changes in each factor.[55, 56] Enhanced levels of fibrinogen, alpha-1-antitrypsin, thrombin/antithrombin III complex, alpha-2 plasmin inhibitor/plasmin complex, and thrombomodulin were documented in claudicants.[57] Compared with healthy control subjects, patients with critical limb ischemia show higher t-PA antigen, PAI-1 antigen, and D-dimer levels both at rest and after exercise. Thrombin formation is enhanced in these patients after submaximal treadmill exercise. Cumulatively, these data suggest that the patients with critical limb ischemia are relatively hypercoagulable. Higher D-dimer levels are associated with poorer functional activity measures,[33] however, the significance of such findings is unknown.[57, 58]

Socio-Economic Effects

Patients with critical limb ischemia have increased functional impairment and increased rates of functional decline compared to those without critical limb ischemia;[10] specifically, they have lower physical activity levels, slower walking speed, poorer balance, and poorer walking endurance.[10, 59] This functional impairment affects quality of life and may lead to an increased prevalence of depressive symptoms that have been observed in patients with critical limb ischemia.[60] Even patients with critical limb ischemia who are asymptomatic have significantly impaired lower extremity function compared with those who do not have PAD.[59]

The economic burden of critical limb ischemia is considerable. Brahmanandam et al.[61] recently reported that patients with critical limb ischemia who underwent revascularization used more health care services after hospital discharge than did patients with noncritical limb ischemia. These services included home health care and transfers to rehabilitation facilities. Independent predictors for increased health care services utilization include older age, female gender, care at a private hospital, longer length of hospitalization, African American race, highest income quartile, and undergoing amputation or debridement.[61] The cost of clinical care for patients with critical limb ischemia in 1990 was estimated at $43,000/patient/year.[62] The mean cost of inpatient hospital treatment during the first 12 months of follow-up in patients undergoing surgical bypass for critical limb ischemia was estimated at £23,322 sterling, which was approximately one-third higher than patients undergoing angioplasty treatment.[63] Others have shown that although there is nearly a two-fold difference in initial cost, the cost-savings of endovascular therapy is not realized over time secondary to subsequent reintervention, particularly in critical limb ischemia patients.[64] Finally, the median cost of managing a patient after amputation is estimated at almost twice that of successful limb salvage.[65] Thus, critical limb ischemia represents a challenging disease state that is associated with considerable morbidity and mortality and a large financial impact on society.

CONCLUSION

Chronic critical limb ischemia is a significant, often under-recognized facet of atherosclerotic disease that has significant medical and functional consequences. A thorough understanding of the systemic risk factors associated with the disease followed by rapid intervention and interruption of the process is necessary to improve outcomes and prevent limb loss and death.

Conflict of Interest Disclosure: The author has completed and submitted the *Methodist DeBakey Cardiovascular Journa*l Conflict of Interest Statement and none were reported.

Funding/Support: The author has no funding disclosures.

Keywords: critical limb ischemia; cardiovascular disease; cardiovascular risk factors; claudication; peripheral arterial disease; amputation

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