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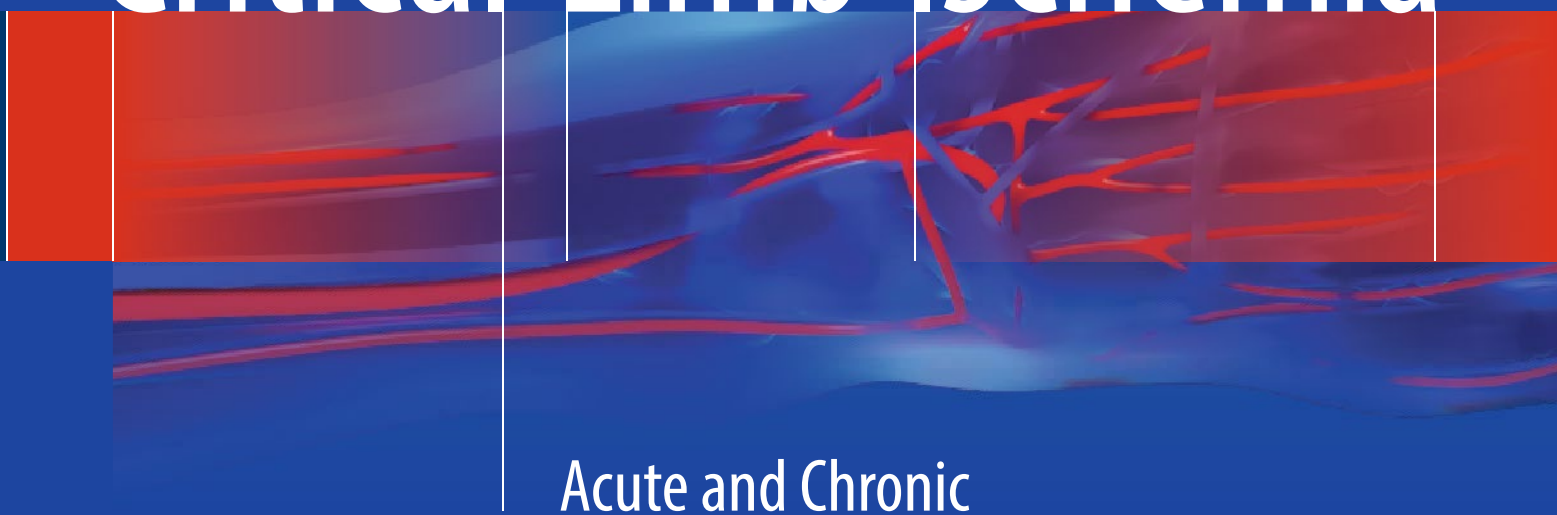
Editors

Critical Limb Ischemia



Acute and Chronic

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To my wonderful wife who has been patient and supportive through all my training and pursuits,
my children who bring a smile to my face every day,
my parents and family who taught me to always strive to do my best,
and to God who makes it all possible.

The Dieters

I dedicate this endeavor to my parents Lakshmidevamma and Nanjundappa who have been wonderfully supportive of my pursuits, without whom, none of this would be possible.

Aravinda Nanjundappa

Foreword

As a long-term colleague and friend of Raymond A. Dieter, Jr., I applaud the superb contributions that he and his sons, Raymond A. Dieter, III and Robert S. Dieter, have made to the art, science, and literature of vascular care. Their careers span the entire gamut of this specialty. Raymond A. Dieter, Jr., is a pioneer of angiography, endovascular procedures, and hybrid surgical/endovascular procedures. Raymond A. Dieter, III is a cardiothoracic and vascular surgeon, and Robert S. Dieter is an interventional cardiologist with an emphasis on vascular disease. Over the past 7 years, the three of them have produced a series of textbooks designed to cover all aspects of this subject: *Peripheral Arterial Disease* (2009), *Venous and Lymphatic Diseases* (2011), and *Endovascular Interventions* (2013). I have had the privilege of writing the foreword to each of these volumes.

This textbook, *Critical Limb Ischemia: Acute and Chronic*, complements the previous volumes by addressing the most severe stage of peripheral arterial disease. Unfortunately, critical limb ischemia (CLI) is one of the most underdiagnosed and undertreated cardiovascular maladies. Patients with CLI have high rates of mortality and morbidity, including limb loss. These patients often are elderly and have serious comorbid conditions, such as diabetes mellitus, heart disease, and cerebrovascular disease. Delays in the diagnosis and treatment of CLI are associated with poor results, including a high incidence of heart attack and stroke. In addition to taking a heavy human toll, CLI is responsible for increased utilization of medical resources. As the average age of the Western population continues to rise, the ravages of this disease can be expected to increase.

In editing this volume, the Dieters were joined by cardiologist Aravinda Nanjundappa. The result is an outstanding textbook that builds on its predecessors and conforms to their high standard. As a guide to the diagnosis and successful management of CLI, this work will be an important resource not only for vascular and endovascular surgeons but also for nonvascular clinicians, who play a crucial role in the early recognition of CLI and prompt referral for specialized care.

Houston, TX, USA

Denton A. Cooley, MD
Founder and President Emeritus
Texas Heart Institute

Preface

This textbook, our fourth on vascular disease and fifth medical textbook overall, is focused on critical limb ischemia. We have purposefully included both acute and chronic conditions in critical limb ischemia. These two disease processes share many common features, yet are unique enough in their presentation and treatment that they deserve separation in their diagnosis and treatment discussions. It is our intent that one volume that covers both entities will be a valuable resource to clinicians.

Although once the sole purview of vascular surgeons, the therapeutics of critical limb ischemia has been significantly advanced through the multidisciplinary approach to the patient and disease. Overall, limb and patient care are enhanced by the current group of specialists who provide care for these patients.

Our book systematically addresses the afflicted patient and the disease process leading to the very real concern—critical limb ischemia—that may torment the patient, the family, and the consulting physician. Loss of an extremity, or a portion thereof, is not necessarily a life-ending process, but it certainly is a debilitating experience whether involvement is of the upper or the lower extremity.

Depending on the etiology, the list of specialties requiring involvement is long, and the required multiple specialty disease/patient physician programs become apparent as the disease progresses. Diabetic, renal, and even oncological consultations are administered concomitantly with the vascular physician, with all working to salvage an extremity, to avoid a prosthesis and lifetime without an arm or leg.

We have included the most frequent as well as the more unusual etiological processes that may lead to the most dreaded concern of a patient and family—amputation. Atherosclerotic diseases of the smoker and the diabetic patient, malignancy-induced occlusive disease, and vasculitic as well as the iatrogenic disorders, while unexpected, are all part of the much larger etiological group endangering the patient and the extremity.

Physicians face these concerns with recognition of the life and lifestyle changes presenting to the family and the patient with extremity ischemia. Diagnosis, diagnostic approaches, and therapeutic options become a major and timely focus for all involved. The multiple disciplines and specialty recognition of the authors and chapter contributors define the majority of the disease complex and the goal for salvage whenever possible.

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Epidemiology of Acute Critical Limb Ischemia

1

Martyn Knowles and Carlos H. Timaran

Introduction

Acute limb ischemia (ALI) is defined as any sudden decrease in limb perfusion causing a potential threat to limb viability [1]. The incidence of ALI is 9–16 cases per 100,000 persons per year for the lower extremity [2–4] and around 1–3 cases per 100,000 persons per year for the upper extremity [5]. Etiology includes embolism, in situ thrombosis with coexisting peripheral arterial disease (PAD), graft/stent thrombosis, trauma, or peripheral aneurysm with embolism or thrombosis. ALI management makes up 10–16 % of the vascular workload for the average vascular specialist. Amputation and mortality rates are historically high in these patients, however, with advances in anticoagulation and surgical therapy that have decreased over time.

Background

Population-based studies have traditionally shown that 3–12 % of the worldwide population suffers from PAD [1, 6–8]. It is estimated that approximately 8 million Americans have impeded lower extremity blood flow, and around half are symptomatic [9, 10]. Smokers, diabetics over the age of 50, renal failure patients, and those over age 70 are particularly at risk [11–14]. Patients with PAD have a significant risk of myocardial infarction, cerebrovascular accident, or death [15, 16]. Symptoms can vary from no symptoms to pain with walking (intermittent claudication), rest pain, and subsequently tissue loss. The majority of patients with claudication will remain stable at 5 years (70–80 %), with 10–20 % developing worsening claudication and only 1–2 % progressing to critical limb ischemia [17].

Critical limb ischemia (CLI) is a more advanced state of arterial occlusive disease, which places the extremity at risk for loss of function, gangrene, or limb loss. In 2003, more than 2.5 million Americans had CLI, which resulted in more than 240,000 amputations in the United States and Europe [18, 19]. Critical limb ischemia can be split into acute or chronic and has different etiologies and natural histories.

Acute limb ischemia (ALI) refers to an abrupt cutoff in the circulation to an extremity—in the absence of trauma or iatrogenic injury—caused by either embolism or thrombosis Cases of CLI with onset <14 days are deemed acute. The significance of ALI is seen in the high limb loss and mortality rates, thus early recognition and treatment is essential to salvage the ischemic extremity [20].

Incidence and Prevalence of Acute Limb Ischemia

The true incidence of ALI is difficult to ascertain. Much of the literature is historical data with no recent updates and has been summarized in multiple texts [21, 22]. Scandinavia has been pivotal in population data regarding ALI. In 1984, Dryjski and Swedenborg [3] investigated the incidence of lower extremity ALI in Stockholm, with a population around 1.5 million. They found an overall annual incidence of nine per 100,000 people. This incidence was related to age; 0.4 per 100,000 for those 20–30 years old, with a peak incidence of 180 per 100,000 in patients over 90. More recently, the Swedish Vascular Registry identified the national incidence of ALI to be 13 per 100,000 people in 1998 [3]. Ljungman et al. focused on temporal trends in ALI over a 19-year period from 1965 to 1983 in Uppsala. They showed an annual increase in ALI from 2.7 to 3.9 %, which remained after age adjustments were made with a 2.7 % annual increase in men [23]. This increase over time was felt to be likely due to an aging population.

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The other major epidemiological data for ALI have originated from British studies. Clason et al. showed in 1989 the incidence for lower extremity ALI in an area of Scotland to be 3.7 per 100,000 [24]. Later, the incidence was assessed from the entire county of Gloucestershire, England, from a single year in 1994. All data was prospectively gathered including hospital and general practice records, for a total population of 540,000. They found that the incidence during that period was one per 7000 and rose to one per 6000 when bypass grafts were included (14.3 per 100,000 and 16.7 per 100,000, respectively) [4].

Acute upper limb ischemia accounts for 16.6 %, approximately one-fifth of all ALI [5]. Upper extremity ALI occurs with an incidence of 1.2–3.5 cases per 100,000 people per year; however, this estimate is an underestimation as it only includes those that underwent intervention [5]. Dryjski and Swedenborg identified a risk of 1.13 per 100,000 people that included all admissions to the hospital. The patients who develop upper extremity ischemia tended to be slightly older than those with lower extremity ALI, with mean ages of 74 compared to 70 [25], and have a higher ratio of female to male at 2:1. The female to male preponderance was noted in a Danish study over a 13-year period that showed the incidence of upper extremity thromboembolectomy was 3.3 per 100,000 person-years among men and 5.2 per 100,000 person-years among women; however, they did not look at any patients that underwent conservative management [26].

Presentation

Campbell et al. showed that 75 % of patients with ALI presented from home, with 10 % coming from another ward or 8 % from another hospital [27]. Only 3 % presented from a nursing home. They additionally noted that 14 % of ALI patients presented with bilateral lower extremity ischemia and that a similar number of left and right legs were affected. Furthermore, Campbell et al. showed that 40 % of patients had a delay in presentation with equal numbers due to patient, primary care physician, and transport delays [27]. Thirty-five percent had a delay in referral to a vascular specialist. There does not appear to be a significant seasonal variation with ALI; however, there is a trend toward a higher presentation in the winter [28].

Patients with ALI present in different stages of severity. Three stages were developed for ALI standardization (Table 1.1) [29]. Stage I is termed "viable." The limb is not immediately threatened, without continuing ischemic pain, without neurologic deficit, and clear audible arterial signal in the pedal arteries. Stage II is termed "threatened." Within this stage there are two levels, split for managing therapies. Stage IIa is marginally threatened and IIb is immediately threatened. Neither have clear audible signals in the pedal arteries. Those patients in IIa will have transient or minimal sensory loss which is usually limited to the toes. Those in IIb have persistent ischemic rest pain, sensory loss above the toes, and any motor disturbance. Stage III is termed "irreversible." These patients have permanent neuromuscular damage with profound sensory loss and muscle paralysis, absent venous, and capillary flow distally. Typically there are skin changes such as skin marbling and muscle. The distribution of the stages of ALI at presentation is shown in Fig. 1.1 [1].

Etiology

The etiology of lower extremity ALI is traditionally either embolism, in situ thrombosis with preexisting peripheral arterial disease (PAD), graft/stent thrombosis, trauma, or peripheral aneurysm with embolism or thrombosis. The frequency of these etiologies is shown in Fig. 1.2 [1, 27]. The timing of presentation depends on the severity of ischemia, which is linked to the etiology. Patients with embolism, trauma, and popliteal aneurysms present early (hours), compared to those with in situ thrombosis presenting later (days) [1]. Reconstructions—either bypass grafts, stents, or angioplasty

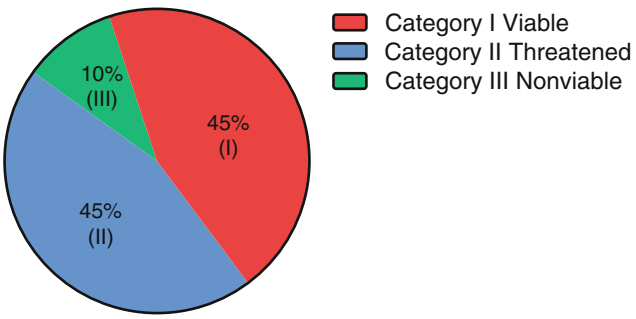

Fig. 1.1 Categories of ALI on presentation. Data from Norgren et al. [1]

Table 1.1 Classification of acute limb ischemia

Ischemic stage	Sensory deficit	Motor deficit	Arterial signal	Venous signal	Treatment
Stage 1	Absent	Absent	Audible	Present	Urgent workup
Stage 2a	None—minimal	Absent	Absent (often)	Present	Urgent surgery
Stage 2b	Moderate	Mild—moderate	Absent (usually)	Present	Emergent surgery
Stage 3	Profound	Profound	Absent	Absent	Amputation

Data from Rutherford et al. [29]

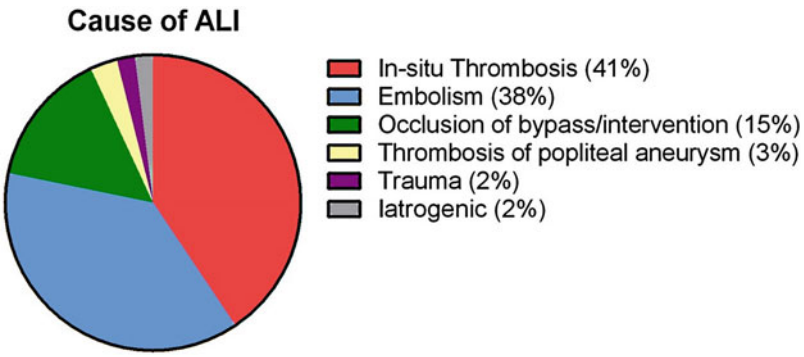

Fig. 1.2 Etiology of acute limb ischemia. Data from Norgren et al. [1] and Campbell et al. [27]

Table 1.2 Differential diagnosis of the mechanism of ALI

Embolism	Thrombosis
Atherosclerotic heart disease	Atherosclerosis
Coronary heart disease	Low-flow states
Acute myocardial infarction	Congestive heart failure
Arrhythmia	Hypovolemia
Valvular heart disease	Hypotension
Rheumatic	Hypercoagulable states
Degenerative	Vascular grafts
Congenital	Progression of disease
Bacterial	Intimal hyperplasia
Prosthetic	Mechanical
Artery to artery	Arterial plaque rupture
Aneurysm	Trauma
Atherosclerotic plaque	Aortic/arterial dissection
Idiopathic	HIV arteriopathy
Iatrogenic	Arteritis with thrombosis
Paradoxical embolus	Popliteal adventitial cyst with thrombosis
Trauma	Popliteal entrapment with thrombosis
Other	Vasospasm with thrombosis (e.g., ergotism, cocaine)
Air	External compression
Amniotic fluid	Iatrogenic
Fat	
Tumor	
Chemicals	
Drugs	

Data from Norgren et al. [1] and O'Connell et al. [30]

sites—can present early or late given whether it is an acute thrombosis or in situ thrombosis with neointimal hyperplasia or atherosclerosis. This timing of presentation is generally related to the presence of or lack of collateral flow, something chronic PAD that typically affords individuals over time. The other differential diagnosis for ALI is shown in Table 1.2 [1, 31]. The typical sites for ALI involvement are shown in Table 1.3 [21, 32].

Upper extremity ALI, in contrast to acute lower extremity ALI, is almost all from embolism, between 72 and 90 % [5]. This is likely due to the relative absence of atherosclerosis in the upper extremities. The heart is the usual source of the embolism, ranging from 58 to 93 %, and atrial fibrillation is the usual etiology [5]. Although the source of the atrial fibrillation has changed from valve disease to ischemic heart disease or myocardial infarction, the incidence has remained relatively unchanged. Other rare causes include atrial myxoma, ventricular aneurysm, cardiac failure, and paradoxical embolus.

Table 1.3 Mechanism of acute limb ischemia according to anatomic location

Sites of limb ischemia	Embolism (%)	Thrombosis (%)
Axillary artery	3	0
Brachial artery	14	3
Aortic bifurcation	3	9
Iliac bifurcation	9	16
Femoral bifurcation	57	53
Popliteal artery	14	19

Data from Hallett et al. [21] and Dryjski et al. [32]

Changing Patterns

Over the last 30 years, there has been a change in the pattern of etiology for ALI. Dryjski et al. identified that 81 % of the cases they saw in their patient population were embolic, and 19 % were thrombotic [3]. In the most contemporary data, embolism now only accounts for 14 % of all cases of ALI [33, 34].

The reasons that arterial embolism has decreased in incidence are multifactorial. There has been a relative decrease of rheumatic fever and subsequently rheumatic heart disease (RHD) in the developed world, though it is still a significant cause of cardiovascular morbidity and mortality in the young in the less developed world. Additionally, aggressive surgical management of rheumatic heart lesions has increased the lifespan and decreased cardiovascular sequelae from RHD. Furthermore, advances in the management of cardiac valve disease and anticoagulation for atrial fibrillation have vastly decreased the number of cardiac embolisms.

Because of the higher prevalence of PAD and an increasingly aging population, arterial thrombosis has increased over time.

Current studies show as little as 9% of ALI cases being caused by embolism [35]. This has, however, not been an acute change with evidence in the decline of embolism since the 1980s. SWEDVASC, the Swedish Vascular Registry, showed a decline of embolism over time from 65 to 43% (Fig. 1.3) [36]. A British study evaluated the management of ALI in 1998 and found that 41% were from thrombosis in situ, 38% from embolism, and 15% from graft or angioplasty occlusion [27]. Luther and Albäck evaluated the population of Helsinki between 1980 and 1991, reporting increases in the frequency of thrombosis by 91% and graft occlusions by 130%, with no change in the incidence of embolism [37].

Current data supports this shift in etiology over time. Ouriel et al. compared the use of urokinase versus surgical intervention for ALI, with thrombosis being the main indication for treatment in 85.6% and embolism in 14.4% [33].

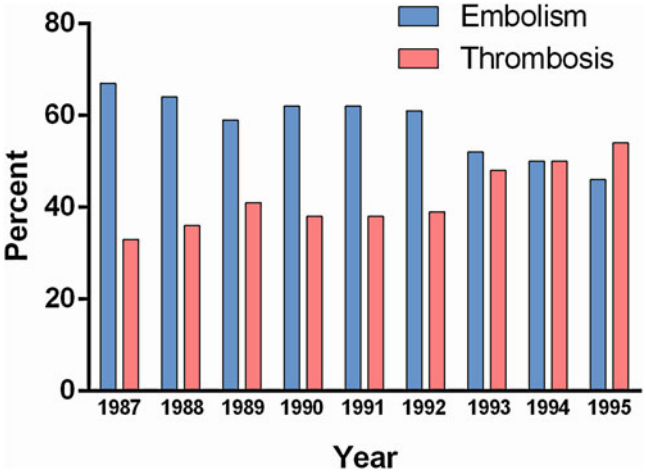

Fig. 1.3 Change in the pattern of embolic and thrombotic disease over time. Data from Bergqvist et al. [36]

Byrne et al. showed the indication for intervention for ALI: thrombosed bypass (36.4%), thrombosed stent (26.6%), native artery thrombosis (24%), embolization (14.3%), and thrombosed popliteal aneurysm (3.2%) [34]. These more current studies show a modern incidence of around 14% for embolism, a stark contrast from 81% in the 1980s (Fig. 1.4).

Natural History

Mortality for lower extremity ALI ranges from 15 to 20% [1]. Major morbidity includes bleeding in 10–15%, major amputation up to 25%, fasciotomy in 5–25%, and renal insufficiency in up to 20%. Campbell et al. evaluated the results from a Vascular Surgical Society of Great Britain and Ireland survey looking at ALI results after 30 days. Thirty-five percent (35%) had died in the follow-up period of 2 years [38]. The cause of death was thromboembolic in 28% including myocardial infarction (15.5%), limb ischemia (5.6%), stroke (4.2%), and mesenteric infarct (2.8%). Further causes of death included cardiac failure (7%), malignant disease (14.1%), and ruptured abdominal aortic aneurysms (2.8%). Twenty-seven percent (27%), however, had an unknown cause of death. Further ALI was noted in 11% of patients; vascular intervention was required in 11% of patients including open surgery, angioplasties, and thrombolytic therapy. Amputation was noted in a further 11% of patients. Of the patients who represented with ALI, 62% required amputations. Survival rates after ALI depend on the etiology. The 5-year survival rate after embolism was 17% and after thrombosis was 44%. This was likely related to an older patient age and higher cardiac risk in the embolism group [30]. Age also appears to affect survival, with older patients doing significantly worse than younger patients. In patients over the age of 80 years, there was an operative

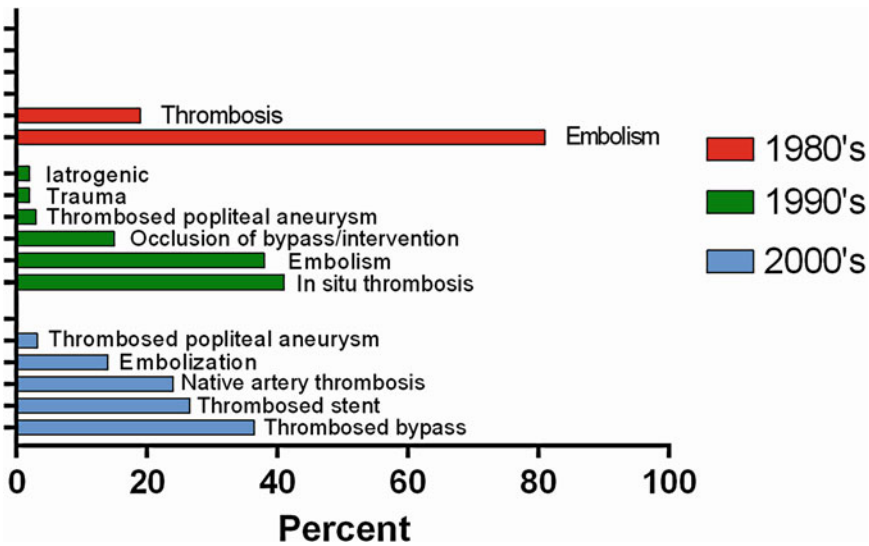

Fig. 1.4 Changes in the pattern of ALI etiology

mortality of 50 %; this is in contrast to 5 % in those under the age of 60 [3].

Acute limb ischemia appears to be a slightly more benign event than lower extremity ALI. Conservative management was undertaken prior to the ability to perform an embolectomy. All patients that had upper extremity ALI maintained their arm without the need for amputation, and in hospital mortality was 17 % [39, 40]. Operative mortality has improved with the use of thromboembolectomy; however, there has been little contemporary data evaluating conservative management.

Results with Intervention

With surgical intervention, morbidity and mortality have traditionally been high. In 1948, a series from Massachusetts General Hospital showed an amputation rate of 71 %, with mostly conservative management [39]. In those that received heparin, 38 % underwent amputation. These poor results early on and the introduction of anticoagulants ushered in nonsurgical management with similar results between anticoagulation and surgery [41]. A later review from the same investigators at Massachusetts General Hospital showed an earlier referral for treatment, subsequent higher surgical treatment, and limb survival of 86 % [42]. Over later years in the 1960s and 1970s, there were increasing numbers of arterial embolectomies after the introduction of a balloon-tipped catheter. In the early experience with embolectomies, only 23 % survived without amputation [43]. In a later experience over 20 years in Sweden, ending in 1999, 1-month survival without amputation was 55 % with arterial embolectomy [44]. Kendrick et al. identified similar mortality and amputation rates and were related to the timing of embolectomy [45]. If the patient was operated on within 6 h of the onset of symptoms, mortality was 15 % and the amputation rate was 4 %. In those that were operated on after 12 h, the mortality rate was 48 % and the amputation rate was 52 %.

With increasing advances in anticoagulation, long-term use of anticoagulation, and operative techniques, operative mortality has improved. In 1998, operative mortality for embolism was 17 % and was 14 % for thrombosis [30]. More recent results show a survival rate of 84 % at 1 year after intervention with a major amputation rate of 15 % [34]. The periprocedural amputation rate was lower at 6.4 %. Time to presentation was noted to be associated with worse outcomes. The risk of amputation was four times higher if presentation was more than 25 h after the onset of symptoms [36].

Thromboembolectomy is the treatment of choice for ALI from embolism. Amputation rates have been 0–8 % since the introduction of the embolectomy balloon with a mortality rate up to 20 %. Recent data suggests a 0–3 % risk of amputation and 0–4.8 % risk of death [26, 46–48]. There is a risk of stroke with upper limb embolectomies of up to 19 % [26]. Greater than 95 % of patients are symptom free after embolectomy, but over time up to 50 % can develop claudication [49]. Recurrent embolization can occur in around 10 % of people who are anticoagulated and 1/3 of those who are off anticoagulation, most likely due to continued atrial fibrillation [50]. Recurrent episodes are associated with higher mortality.

Summary

Acute limb ischemia is a harbinger of significant morbidity and mortality. Despite advances in the medical and surgical treatment over the last century, limb amputation and mortality remain high. Furthermore, long-term follow-up of patients after ALI show a significant risk of cardiovascular morbidity and loss of life. The etiology for lower extremity ALI has changed over the last 30 years, with a decrease in the rate of embolic events, likely related to aggressive anticoagulation for valvular and cardiac complaints. Embolism remains the predominant cause of upper extremity ALI. Vascular intervention for ALI is a significant part of any vascular practice and is likely to increase in an aging population. Expeditious presentation and operative management, whether with open or endovascular techniques, yield the best results.

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Epidemiology of Chronic Critical Limb Ischemia

2

Akhil Gulati, Lawrence Garcia, and Subasit Acharji

Introduction

Peripheral artery disease (PAD) is often referred to as a continuum of disease of occlusive arterial syndromes that can range from asymptomatic obstructive disease through occlusive disease requiring amputation. This entire spectrum of PAD has prevalence as high as 20 % of the general population [1]. This spectrum becomes more progressive and symptomatic as the disease causes an imbalance of distal perfusion pressure to the tissue and metabolic demands within that tissue. On the latter end of this continuum, chronic critical limb ischemia (CLI) has a prevalence that is more difficult to define and is quite variable in the published literature. Unlike asymptomatic PAD or exertional claudication, CLI occurs with inadequate perfusion at rest [2].

Like most of the terminology of peripheral vascular disease, the definitions of CLI have evolved over the years, with first an increasing need to classify the entire continuum of PAD, the need to further classify those undergoing surgical procedures, and then to include more objective measures as well as the clinical presentation. In this chapter, we will discuss the epidemiology of CLI. We will present the historical background of CLI and the risk factors along with its clinical presentations and then after the epidemiology and prevalence of CLI along with its risk stratification and prognostic data before discussing the socioeconomic impact of this disease.

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Definition of Chronic Critical Limb Ischemia

The definition of CLI has evolved over time. It has been classically defined as greater than 2 weeks of extremity rest pain, ulcers, or extremity gangrene, secondary to objectively proven peripheral artery disease. In its most extreme case, CLI can lead to limb loss [1, 2].

Several criteria are often used for objective evidence of CLI, but most commonly involve: (a) ankle-brachial index (ABI) of 0.4 or less, (b) ankle systolic pressure of 50 mmHg or less, (c) toe systolic pressure of 30 mmHg or less, (d) toe-brachial index (TBI) of 0.25 or less, and (e) reduced supine forefoot transcutaneous oxygen pressure (TcPO2) less than 30 mmHg [3, 4]. Although not an exact definition, CLI would be seen as corresponding with stages III and IV of Fontaine Classification and categories 4 through 6 of the Rutherford classification system [5, 6] (see Table 2.1).

While the Fontaine and Rutherford classification systems originally were implemented to categorize peripheral arterial disease by symptoms several decades ago, objective criteria were adapted as technology has developed and several consensus documents have then evolved the definition of CLI [7].

The first consensus document was the Second European Meeting Consensus Document on CLI (1991) that used two definitions for CLI based on clinical use and on research use [4] as written below:

1. CLI, in both diabetic and nondiabetic patients, is defined by either of the following two criteria:
   a. Persistently recurring ischemic rest pain requiring regular adequate analgesia for more than 2 weeks with an ankle systolic pressure ≤50 mmHg and/or toe systolic pressure ≤30 mmHg
   b. Ulceration or gangrene of the foot or toes, with an ankle systolic pressure ≤50 mmHg or toe systolic pressure ≤30 mmHg
2. A more precise description of the type and severity of CLI is also necessary for the design and reporting of

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Table 2.1 Fontaine's stages and Rutherford categories for lower limb symptom classification

Fontaine's stages		Rutherford categories		
Stage	Clinical presentation	Grade	Category	Clinical presentation
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	I	Mild claudication
IIb	Moderate to severe		2	Moderate claudication
	Claudication		3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
			6	Major tissue loss

clinical trials. In addition to the above definition, the following information is also desirable:

a. Arteriography to delineate the anatomy of the large vessel disease throughout the leg and foot
b. Toe arterial pressure in all patients, including those who are not diabetic
c. A technique for quantifying the local microcirculation in the ischemia area (e.g., capillary microscopy, transcutaneous oxygen pressure [TcPO2], or laser Doppler)

There has been some debate on the value of ankle pressures. However these definitions have been generally agreed upon as the threshold to be used.

The next large summary consensus was the Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease (2000) that did continue the method of having a clinical definition, as well as a research definition. It also changed the thresholds for some of the objective criteria [8]:

1. Clinical definition of critical limb ischemia (CLI): The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. The CLI implies chronicity and is to be distinguished from acute limb ischemia.
2. Trials and reporting standards definition of CLI: A relatively inclusive entry criterion is favored, the aim being to ensure that the ulceration, gangrene, or rest pain is indeed caused by peripheral arterial disease and that most would be expected to require a major amputation within the next 6 months to a year in the absence of a significant hemodynamic improvement. To achieve this, it is suggested to use absolute pressures of either ankle pressure <50–70 mmHg or toe pressure <30–50 mmHg or reduced supine forefoot TcPO2 <30–50 mmHg.

Here, there is an emphasis on CLI being defined by symptoms and showing objective-proven arterial occlusive disease. The thresholds for ankle pressure were raised, possibly to answer some of the critics of the 1991 European Consensus Document. However, the toe pressure and TcPO2 pressure thresholds were also raised.

The ACC/AHA created practice guidelines in 2005 for management of patients with peripheral artery disease and also addressed the definition of CLI using some of the other consensus statements [9]. It uses the TASC clinical definition as above and points out that most vascular clinicians would define CLI as those patients in whom the untreated natural history would lead to a major limb loss within 6 months [9].

The most recent consensus statement is the TASC Document that was updated (TASC II 2007) that simplified the definition: "The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease. The term CLI implies chronicity and is to be distinguished from acute limb ischemia" [3]. It also stresses that ischemic rest pain will most often occur with ankle pressures <50 mmHg and toe pressures <30 mmHg but that in situations where healing is needed (if a venous or traumatic ulcer is not healing well due to poor arterial flow), often ankle pressures less than 70 mmHg and toe pressures less than 50 mmHg are insufficient [3]. There is not complete consensus as to the objective vascular parameters to be used for CLI, but the thresholds we have mentioned are the most commonly used in various clinical practices, as well as for various research articles and publications.

CLI is most often caused by, and associated with, obstructive atherosclerotic arterial disease. While most risk factor modification, research, and focus are on this disease process, it is important to note that since CLI results from the imbalance between supply of nutrients and metabolic demand in distal tissues, there are other causes that can result in CLI. Other causes can include atheroembolic/thromboembolic disease, thrombosis resulting from hypercoagulable states, vasculitides, thromboangiitis obliterans, cystic adventitial disease, Buerger's disease, thoracic outlet syndrome, popliteal entrapment syndrome, trauma, and more [9, 10]. There are also multiple risk factors to CLI as well as contributing factors to the acceleration of the disease process that will be addressed elsewhere.

Epidemiology of Chronic Critical Limb Ischemia

Peripheral arterial occlusive disease has been well studied over the last several decades with most research dealing with symptomatic disease, including intermittent claudication through the extreme of limb loss. It has been noted that there is a prevalence of 8–10 million Americans who suffer from arterial occlusive disease [3]. While the reported prevalence

of peripheral arterial disease (PAD) may depend on the particular population studied, and the modality used to diagnose it (subjective and objective criteria), if one uses PAD to be defined by an ankle-brachial index of <0.90, then it may likely be present in up to 4–10 % of patients in the USA and Europe [11–13] and involving a prevalence of an estimated 27 million people in those same areas [14].

There is widespread data about the incidence and prevalence of PAD as an entity; however, there is limited data regarding chronic critical limb ischemia. It is difficult to obtain specific epidemiologic data for CLI for several reasons [7]. First, the identification of CLI is more difficult than identifying some other conditions (like PAD as defined by ABI <0.90). As stated above, a general definition that most clinicians use is by attributing rest pain, ulcers, or extremity gangrene to a peripheral arterial occlusive disease, and that lasts longer than 2 weeks. This requires a level of proficiency and diagnostic assessments that are not often readily available in large epidemiological studies [7].

Secondly, as noted, the definition of CLI has evolved over time. There is a heterogeneity of many studies using different definitions and often without the objective parameters to define that CLI has been published. There are often major differences between the various studies that can make the data inconsistent. Lastly, the actual numerical epidemiological data that is usually used and cited is often inferred from other markers, such as the incidence of amputations (which assumes that a quarter of CLI patients undergo this procedure). Data is often presented from assumptions of the natural history of PAD (i.e., perhaps the estimate that 5–10 % of patients with either asymptomatic PAD or claudication will go on to become CLI at 5 years time) [3, 7].

An Italian study by Catalano et al. tried to confront the difficult problem of getting accurate epidemiological data for CLI [15]. The study used three different methods to obtain data. They first created a prospective study on the incidence of CLI in 200 patients who had been suffering from claudication and in 190 controls that showed an incidence of 450 per million people per year for CLI and 112 per million people per year for amputations in those above the age of 45. They also did a 3-month prospective study on CLI hospitalizations in a sample of hospitals in Lombardy, Italy (Northern Italy region), that showed an incidence of 642 per million people per year for CLI and 160 per million people per year in those over the age of 45. Lastly, they also looked at the number of amputations performed in hospitals of two regions (6 years in Lombardy and 2 years in Emilia Romagna) that showed an incidence of 577 per million people per year for CLI and 172 per million people per year for amputations in Lombardy and 530 per million people per year for CLI and 154 per million people per year for amputations in Emilia Romagna. Interestingly, the results revealed an incidence of both CLI and amputation rates that were lower than expected, with authors suggesting this to be explained by the area of Italy studied being one with a known high rate of "cardiovascular protection" [15].

While epidemiological data may be difficult to obtain, compare, and contrast, much of the data that is available is still fairly useful and reveals the scope of the disease, the natural history of PAD, and the serious effects of CLI and the socioeconomic impact of this disease.

The TASC II guidelines have estimated that the incidence of CLI, as inferred from the natural history of PAD and amputation rates, is approximately 500–1000 per million per year in a European or North American population (150,000 cases per year in the USA) [3]. As noted, some of the large prospective population studies have shown an incidence of 220 new cases per million per year in the general population [15, 16]. The prevalence of CLI is often estimated between 0.5 and 1.2 % in various studies and registries. One particular European cross-sectional study done in Sweden used an age-standardized randomly selected population sample of men and women aged 60–90 years with 5080 subjects included (64 % participation rate) to answer questionnaires on medical history, medication, and symptoms as their ABI was also measured [17]. The study also gave special attention to critical limb ischemia and gender differences. The prevalence of CLI was found to be approximately 1.2 %, with women having a slightly higher prevalence than men (1.5 % vs 0.8 %, $p < 0.008$), although other studies may show the opposite. This study also showed that prevalence of CLI increased as age increased, as one would expect.

In attempting to determine the prevalence of CLI and the risk factors associated with developing CLI, the largest published population study was done in Norway (HUNT 2 Study) between 1995 and 1997 with a questionnaire for the 20,291 participants between the age of 40 and 69 that was specifically aimed at identifying CLI [18]. Questionnaires were sent to all patients over age 20, but the focus was on those 40–69 years of age, and thus the study population consisted of 9640 men and 10,651 women. For the purpose of the study, CLI was defined as having ulcers on toes, feet, or ankles that have failed to heal or persistent pain in the forefoot while in the supine position but with relief of the pain when standing up. The study revealed a prevalence of CLI in this population of 0.24 % (0.26 % for men and 0.24 % for women), with the age-adjusted prevalence of CLI increasing with age as expected. Tobacco use conferred a 2.3 times increased risk of CLI compared to those participants who never smoked, and diabetes mellitus conferred a 4.4 times increased risk of developing CLI compared to the general population. Other risk factors that were independently associated with increased risk of CLI included older age, elevated total cholesterol, elevated serum triglyceride, higher body mass index (BMI), and angina. The prevalence of CLI was found to be 2500 per million inhabitants, similar between

both genders and increasing with age. The study did note, however, that it may be easier and necessary to identify CLI by symptoms and clinical signs (rather than with objective measurements). This does cause drawbacks where one may include patients with non-PAD ulcers or pain in the CLI category. The study may also include some patients with acute limb ischemia (ALI) in the CLI category by the questions that were used in the questionnaire.

Another study was a population-based, prospective cohort study of the comparative value of modern risk stratification techniques for cardiac events and studied 4814 subjects aged 45–75 [19]. As part of this study, PAD was assessed by obtaining ABI and peak ankle artery pressures for all patients, and this data was used (along with patient acknowledging a history of specific PAD or CLI) to determine prevalence. In this study, CLI was considered present if the highest ankle artery pressure measured <70 mmHg. The prevalence of CLI in this population was 0.11 % with a trend toward increased association with age. The study did have some limitations that may have lowered the prevalence by not including some of the more severely ill subjects, not including the subjects that could not get an ABI performed (patients with ulcers or wounds that would already qualify them as CLI subjects) and the overall low response rate that may have been a selection bias against CLI, as well.

The TASC II study noted that 5–10 % of patients with asymptomatic PAD or claudication will progress to CLI within 5 years. Up to 1–3 % of patients with PAD present initially with CLI [3]. This group is often characterized as patients who are older or sedentary and thus have not exerted themselves to get claudication symptoms. Also, these are often patients with sensory neuropathy or patients with other medical issues such as heart failure. Some studies have shown that possibly half of CLI patients in the general population may not have any PAD symptoms even 6 months prior to the onset of clinical CLI [7, 20].

CLI is the initial clinical presentation in only 1–3 % of PAD cases, although arteriographic progression has been documented in up to 60 % of PAD patients after 5 years of follow-up. Other studies have shown that 40–50 % of those affected present with atypical leg pains, 10–35 % with intermittent claudication, and 20–50 % with no symptoms at all [9, 21].

One of the studies that attempted to show the natural history of those with intermittent claudication was the Edinburgh Artery Study in 1988, where 1592 participants between ages 55 and 74 were randomly selected and the presence of PAD was determined by questionnaire on claudication, ABI and a reactive hyperemia test. This cohort was then followed over 5 years for subsequent vascular events. In this cohort, 116 new cases of claudication were identified, and of those 4.1 % underwent vascular surgery/arterial reconstruction, 4.1 % underwent amputation, and 1.4 % developed leg ulceration at 5 years time [22]. Limitations in this study were the small incidence noted of intermittent claudication in the population and the variable regional practices regarding when to perform amputation.

A much larger and longer study was done over a 15 year period by Aquino et al. who collected data on 1244 men with intermittent claudication with a mean follow-up of 45 months (with some statistically valid data followed for as long as 12 years) [23]. The group collected data on demographics, clinical risk factors, ABI and serially followed ABI, self-reported walking distance, and monitored patients for ischemic rest pain and ischemic ulceration. Results revealed that ABI declined an average of 0.014 per year. The cumulative 10-year risk of development of ischemic ulcers was 23 %, and the 10-year risk of ischemic rest pain was 30 %. Lower ABI and diabetes mellitus were identified as significant predictors of ischemic ulcers, with smoking added as a predictor as well for ischemic rest pain. The study was limited by only following a male population (study done at a Veterans Administration Center), and there was possibly a selection bias (in that it may be likely that sicker patients were the ones referred to the vascular lab). Of note, the study also identified a particularly higher risk of limb event subset of patients who were diabetic with ABI < 0.3 [24, 25].

Risk Factors, Stratification, and Prognosis of Chronic Critical Limb Ischemia

Chronic critical limb ischemia (CLI) is the result of atherosclerotic peripheral arterial occlusive disease and thus shares many of the same risk factors of atherosclerotic disease in other vascular territories. The risk factors include hypertension, hypercholesterolemia, cigarette smoking, and diabetes mellitus. The latter two are more strongly associated with progressive CLI than others [3]. Diabetic patients develop early onset and more rapidly progressive disease with the involvement of distal vessels. The aorta and iliac arteries are relatively spared when compared to profunda femoris and popliteal and tibial arteries, which may be less amenable to revascularization, thus along with presence of diabetic neuropathy leads to higher rates of amputation compared to nondiabetic. Similarly among smokers, the risk of developing CLI increases directly proportionally to the amount of cigarettes smoked [26].

Transcutaneous oxygen tension (TcPO2), determined by blood flow and arterial oxygen tension (PaO2), can be a marker of total distal runoff (arterial and arteriolar runoff) or perfusion reserve in forefoot and may predict changes in blood flow to an extremity when flow is severely restricted [27]. Recently a risk stratification tool based on TcPO2 has been suggested [7]: