Is revascularization and limb salvage always the best treatment for critical limb ischemia?

Mark R. Nehler, MD,a William R. Hiatt, MD,b and Lloyd M. Taylor, Jr, MD,c Denver, Colo; and Portland, Ore

Contemporary care of critical limb ischemia (CLI) consists of near universal attempts at aggressive limb salvage. In our opinion this approach is excessively lesion focused and inadequately patient focused. Subgroups of the CLI population currently undergoing extensive limb salvage efforts may be better served with primary amputation or nonoperative management. We describe limitations in the knowledge base underlying modern care of CLI.

First, our understanding of the natural history of CLI is limited, with minimal ability to identify at-risk patients and prevent disease progression. Most patients with symptomatic CLI have a tremendous disease burden, with poor baseline function, including loss of ability to ambulate and ability to live independently in many and abbreviated survival for most. Second, surgical treatment is graft and limb focused, with only modest understanding of the effects of treatment on patient morbidity and function. While surgical revascularization may prevent limb loss, this outcome does not universally result in ambulation or functional independence. Third, the advantage of revascularization over primary amputation in patients who do not regain independent ambulation is unclear. Fourth, the influence of the extent of ischemic foot lesions on overall outcomes has not been clearly defined. Finally, even if limb ischemia can be relieved, a critical concern remains the high cardiovascular mortality risk in the CLI population. We do not know if cardiovascular risk factor modification can modify this natural history. We do not know whether a chronically ischemic limb may actually increase the systemic risk for myocardial infarction or stroke by inducing a proinflammatory state and generating reactive oxygen species. What is clear is that further study of CLI is needed in the form of clinical trials with patient-oriented rather than limb-oriented outcomes. We will briefly examine the reasons for each of these statements. We will then propose an approach to addressing acquisition of the data relevant to each issue, including proposal for some relevant clinical trials.

NATURAL HISTORY OF CLI

One of the greatest deficiencies in the modern understanding of CLI is the antecedent natural history. The Fontaine classification system designates CLI as either stage I (asymptomatic), stage II (claudication), stage III (rest pain), or stage IV (tissue necrosis). Many clinicians assume that CLI progresses through these stages in a stepwise manner. However, multiple natural history studies of Fontaine II disease reveal that in very few patients does claudication ever progress to CLI and that only 4% of patients are at risk for limb loss. A paradoxical exception to this rule occurs when patients with claudication undergo surgical revascularization. Subsequent failure of the angioplasty or bypass graft places that patient at increased risk for development of CLI. Thus in most patients CLI progresses directly from Fontaine stage I to stage III or IV. Dormandy et al demonstrated in a multicenter prostaglandin trial that 50% of enrolled patients were asymptomatic 6 months before major amputation because of CLI. McDermott et al demonstrated that many patients traditionally classified as having Fontaine stage I disease are not asymptomatic but manifest a variety of lower extremity symptoms other than claudication not currently considered typical symptoms of lower extremity vascular disease. The extensive comorbid conditions that accompany CLI in many patients, eg, diabetes, coronary artery disease, and chronic obstructive pulmonary disease, may restrict their activities sufficiently to preclude any claudication before CLI onset. The most reproducible natural history data from the surgical literature of CLI report a 50% to 60% 5-year patient survival rate, but in selected series survival was lower. Patients with CLI and end-stage renal disease have an even worse survival rate. In view of this markedly increased mortality, surgical care for most patients with CLI must be considered highly palliative. Obviously, the risk-benefit ratio for interventions in asymptomatic conditions in this
population (eg, coexistent carotid disease, graft surveillance) needs to be carefully weighed. Equally important is weighing the potential morbidity of therapy in palliative care. Currently unanswered questions include the following: Is it really acceptable to strive for the greatest patency and limb salvage rates in a population with abbreviated survival when doing so frequently is associated with significant morbidity? Is it reasonable to have up to 10% to 15% mortality before incision and target wound healing? Is CLI, in reality, more important as a marker for early mortality from end-stage atherosclerosis and the initial symptom of limb threat actually a secondary consideration?

EXAGGERATED ROLE OF REVASCULARIZATION

We believe the reported success for lower extremity revascularization for CLI can be summarized as follows: (1) Modern anesthesia and perioperative care have reduced operative mortality rates to 5% or less. (2) Centers of excellence report 5-year assisted primary patency rates of 70% to 90% for bypass grafting to the above-knee and below-knee popliteal arteries using saphenous vein (reversed or in situ). Similarly, 5-year assisted primary patency rates of 60% and greater have been reported for tibial and pedal bypass grafting using saphenous vein. Slightly reduced 5-year patency rates have been reported for alternate vein bypass grafting, with up to 30% need for graft surveillance revisions. (3) Multiple operative series demonstrate 5-year limb salvage of 80% and greater. The current surgical database regarding the efficacy of lower extremity revascularization needs to be placed in perspective. Clearly, large referral centers in multiple geographic locations have reported excellent technical results in preserving limbs using alternate vein conduits, spliced vein segments, and conducting distal anastomoses to tibial and pedal targets.

However, when scrutinized, these data reflect only a subgroup of the vascular centers in the United States most expert in the management of CLI. Most of these reports arise from a handful of very active centers within this subgroup. Thus these reports may lack generalizability. The actual state of the art regarding lower extremity revascularization throughout the United States (and Europe) is less clear. Evidence from statewide Medicare surveys regarding carotid endarterectomy indicates that the highly expert referral centers are actually the outliers nationwide, and global efficacy is less than the “best” reported surgical series. It would be reasonable to assume a similar situation with regard to lower extremity arterial bypass grafting.

Lower extremity arterial bypass surveillance programs have been widely accepted based on work from expert centers demonstrating efficacy in predominately asymptomatic graft lesion detection and repair. However, graft surveillance can be considered a postoperative morbidity because it increases the effects on the patient and the cost of the procedure. Despite the reported success with graft surveillance, no randomized trials clearly demonstrate that aggressively treating all asymptomatic graft lesions leads to an increase in graft patency and limb salvage. Although many experts believe a randomized trial is unnecessary, one must keep in mind the early skepticism regarding the need for the recently reported Veterans Affairs Small Aneurysm Trial. One fact that is indisputable is that these are usually asymptomatic lesions in patients with limited life expectancy who are then undergoing potentially morbidity procedures.

The study of the chronic morbidity of revascularization because of CLI is in its infancy. It appears that up to 25% of patients have some type of incisional wound complication postoperatively. Some require repeat operations, and all bear the pain and expense of extensive wound care. In up to 1% of patients who undergo revascularization a graft infection will develop secondary to wound breakdown, with a 15% mortality rate and 40% incidence of major limb loss. Postoperative lymphedema is considered an important factor in prolonging incisional healing and patient discomfort. Control of pain is clearly a critical issue for palliative care, yet the incidence of postoperative ischemic neuropathy, iatrogenic operative nerve injury, and the effect of chronic nonhealing incisional and foot wounds are little understood.

ROLE OF PRIMARY AMPUTATION STRATEGIES: IMPACT ON FUNCTION

There are similar deficiencies in our knowledge regarding amputation because of CLI. The above-knee amputation (AKA)–below knee amputation (BKA) ratio is roughly 1:1 and has not changed in several decades. The perioperative mortality rate for BKA is 5% to 10% and for AKA is 10% to 15%, due to comorbid conditions in the population with end-stage disease currently receiving this therapy. Primary incisional healing is far greater with AKA than with BKA. In as many as a third of BKA procedures, secondary operations will be required in an attempt to achieve healing, and half of these ultimately will be converted to AKA. Independent amputation at 1 year in vascular amputees is negligible for AKA and 10% to 25% for BKA, with a steady attrition rate over time due to multiple factors.

Despite these data, the functional status and level of independence in the CLI population is largely unknown. Extensive comorbid conditions, eg, diabetes, cardiac disease, and pulmonary disease, likely limit amputation even in the absence of ischemic rest pain or ulceration. Thus even a successful operation or angioplasty may not improve functional status or relieve suffering in all patients. Most vascular surgeons would agree that an edematous extremity with some degree of pain and slowly healing wounds is a reasonable expectation for the first 3 months after successful revascularization. Some of these patients will recover with minimal additional problems and survive for many years. However, in selected high-risk patients an early amputation with the remainder of the patient’s life focused on home and social activities may be time better spent than weeks of hospitalization to repair failed distal bypass procedures or in...
EFFECT OF ISCHEMIC ULCERATION ON OUTCOME

Very little is known regarding the degree to which the extent of foot lesions influences morbidity, ultimate success, and functional outcome of limb salvage attempts in patients with CLI. Selected reports describe collective series of lower extremity bypass procedures with mid-foot amputation and free-flap tissue transfer to salvage extensively involved lesions of the forefoot or heel, but these approaches must currently be considered the exception rather than the rule. Aggressive foot salvage in CLI with severe necrosis frequently requires multiple foot operations, prolonged wound care, and healing time measured in months rather than weeks. It seems intuitive that there is a point where the morbidity of this approach exceeds any long-term benefit. A tremendous amount of research has been focused on defining pedal circulation limits (e.g., toe pressure, pulse volume recordings, transcutaneous oxygen tension) that would be adequate to support local wound healing, with minimal consideration of the nature of wounds this marginal circulation should support.

EFFECT OF SYSTEMIC ATHEROSCLEROSIS ON OUTCOME

Could aggressive risk factor modification in patients with CLI improve 5-year survival rates, or do these patients have such extensive systemic atherosclerosis that their mortality risk cannot be modified? Does chronic lower extremity ischemia manifest by unhealed wounds, graft thrombosis, or stenosis actually promote fatal ischemic events in this population because of a systemic inflammatory state with oxygen free radical generation that promotes coronary plaque instability? Evidence in the coronary literature supports this mechanism. Is there actually an inverse relationship between limb salvage and survival in patients with CLI? Would survival actually be improved by a more judicious approach to high-risk revascularization (tenuous revascularization due to conduit or target arteries, or large foot lesions), resulting in early amputation of some limbs at high risk for recurrent or ongoing ischemia? We currently do not have data to permit a definitive answer to any of these important questions.

PROPOSED APPROACH TO PATIENT MANAGEMENT

If subgroups of patients with CLI are better served by amputation, how can they be identified? A possible approach is to look at the problem from three sides: technical issues of revascularization, foot wound healing issues, and comorbidity. Patients with marginal prospects in more than one category would not be considered reasonable revascularization candidates. Therefore alternate vein conduit for a tibial bypass would be reasonable for a patient with manageable toe gangrene and modest comorbidity, but would not be reasonable for a patient receiving home oxygen therapy or with a large heel defect. Subgroups with severe comorbid conditions, who may survive the procedure because of modern anesthesia but are unlikely to survive the follow-up required to heal incisions and wounds and the rehabilitation process, would also not be offered extensive limb salvage. Perhaps other clinical markers are needed. Preoperative C-reactive protein levels have been used to predict patient survival, foot healing, and limb salvage. Low serum albumin levels have correlated with mortality and increased length of stay in multiple studies of elderly hospitalized patients. We are not aware of any reports examining this marker in a series of distal bypass procedures.

Prospective natural history studies are needed to close the gap between asymptomatic patients with significant arterial occlusive disease and patients with CLI. Screening for patients with Fontaine I disease with significantly reduced ankle brachial indices with or without other risk factors and then observing them for onset of CLI in a multicenter study would greatly enhance our currently limited data base by providing insight into at-risk populations. A randomized trial of graft surveillance is in order. Multicenter clinical trials of limb salvage versus amputation in high-risk groups (e.g., patients with renal failure, repeat operations, extensive foot necrosis, poor nutrition, extensive comorbidity) focusing on wound healing and function are needed. Similar trials for aggressive risk factor modification (e.g., anti-platelet, lipid control, blood pressure control) and mortality reduction in CLI populations are in order.

Clinical data are always available for the comorbid conditions our patients have, but do we really use this information in practice? Does a patient’s nutritional status, pulmonary status, ejection fraction, body mass index, or hemoglobin level, all of which have tremendous functional and some survival implications, really factor into our decision making about limb salvage? Or is our attention forever fated to be concerned only with availability of autogenous conduit and the arteriographic findings? The late Dr. John Porter stated on more than one occasion, “The last three decades in limb salvage surgery we discovered what we could do. Now it is time to learn what we should do.”

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