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EDITORIAL COMMENT

Pathology of Arterial Disease in Limb Loss

The Clot Thickens*

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The pathobiology of limb ischemic events in patients with peripheral artery disease is complex. The severity of arterial stenoses correlates with reduced limb perfusion, and if the supply of oxygen and nutrients is sufficiently limited, limb ischemia occurs, threatening tissue viability. Atherosclerosis is the principal cause of peripheral artery disease, and it is reasonably presumed that atherosclerotic plaque accounts for luminal narrowing in most circumstances. Yet, atherosclerosis alone does not adequately explain development of limb ischemia in patients who had previously been asymptomatic or experiencing intermittent claudication. Thrombosis, when superimposed on atherosclerotic plaque or formed downstream from an arterial occlusion, may hasten the development of ischemia. Moreover, the risk of ischemic limb events is ~4 fold higher in PAD patients with prior lower extremity revascularization, particularly bypass grafting, implicating the occurrence of graft thrombosis (1,2).

Recent trials in patients with peripheral artery disease have assessed the incidence of adverse limb events with greater specificity, and found robust reductions in limb ischemic events with novel antithrombotic strategies. The addition of the protease-activated receptor antagonist vorapaxar, which inhibits thrombin mediated platelet activation, to a background of aspirin, $P2Y_{12}$ inhibitors, or both in patients with peripheral artery disease decreased major adverse limb events by 30%, including acute limb ischemia and limb revascularization (3). The combination of low-dose rivaroxaban and aspirin compared with aspirin alone resulted in a 46% reduction in major adverse limb events, including acute limb ischemia, revascularization for ischemia within 30 days, or ischemic amputation (4). The results of these trials underscore the likelihood of thrombosis as a causal mechanism for these events.

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The paper by Narula et al. (5) in this issue of the *Journal* adds important descriptive information in this regard. The authors describe arterial pathology in 299 arteries derived from 95 patients: 75 of whom are described as having chronic critical limb ischemia as the reason for their amputation, 3 as a consequence of acute limb ischemia, and the remainder had amputation for other nonvascular reasons. The majority were below knee amputations. Several key observations of the study were that the nature of arterial disease differed by location, with greater atherosclerotic burden in proximal (femoral and popliteal) arteries, and more fibrocalcific disease and medial calcification in distal (infrapopliteal) arteries. Thrombotic occlusion of femoral-popliteal arteries was more likely to be associated with significant atherosclerosis, whereas in infrapopliteal arteries, it was more likely to occur in the absence of significant atherosclerosis. In addition, acute and chronic thrombi were found in both distributions, but acute thrombi were found more frequently in proximal arteries and chronic thrombi appeared more frequently in distal arteries. Thus, a key pathophysiological issue

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highlighted by this study is the role of thrombosis in the progression to critical limb ischemia and the risk of amputation.

By its nature, this pathological study is retrospective, and focused on limb vascular findings from amputated limbs. It would be useful to have correlative information on patient characteristics and comorbidities, conditions that are likely to affect vascular pathology. For example, one would expect that medial calcification would be more frequent in patients with chronic kidney disease and/or diabetes than in those without. Similarly, acute embolic occlusion of arteries would be more likely in patients with atrial fibrillation or aortic atherosclerosis or aneurysms. It would also be interesting to know how many patients had previously undergone limb revascularization procedures, and if present, the pathological findings of bypass grafts.

The authors observed acute thrombi in proximal arteries and hypothesized that these findings might represent embolic disease. Other causes for thrombus formation should also be considered, even in areas with so-called insignificant atherosclerosis, including endothelial damage and plaque erosion, and in some occasions, ruptured fibroatheromatous plaque, as occurs frequently in coronary arteries of patients presenting with myocardial infarction. The study observed a high frequency of chronic thrombi in distal infrapopliteal vessels, a finding that may reflect emboli from more proximal arteries or in situ thrombus consequent to poor flow and intima-medial abnormalities of the vascular wall.

It would be simplistic to conclude that poor perfusion due to conduit artery obstruction is the sole cause of limb ischemia leading to amputation. The pathophysiological mechanisms are much more complex than the hemodynamic compromise caused by arterial lesions and depend in part on the patient's risk factors and comorbidities. Microvascular disease, endothelial dysfunction, altered hemorheology, impaired angiogenesis, and systemic inflammation are likely to contribute, depending in part on the patient's risk factors and comorbidities (6). In patients with diabetes, for example, microvascular disease may impair blood flow to the foot and cause neuropathy with the associated risk of neuropathic ulcers (7). In addition to ischemia, the severity of wounds and the presence of infection and necrosis adversely affect limb viability (8). Ongoing research, such as that supported by the American Heart Association's Vascular Disease Strategically Focused Research Network, seeks to further elucidate the pathobiology and predictors of chronic limb ischemia.

The study by Narula et al. (5) is an important step forward in furthering our understanding of the complex pathology contributing to amputation in patients with peripheral artery disease. Further research is needed to elucidate the pathobiology and predictors of limb ischemia so that targeted preventive strategies may improve limb outcomes and decrease the risk of amputation.

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