Atherosclerotic peripheral artery disease (PAD) is common, estimated to affect 4.3% to 29% of the adult population. PAD is an important syndrome to identify promptly because it is associated with an increased risk of premature myocardial infarction, stroke, and all-cause mortality. The public has limited appreciation for the disorder and its associated risks, making awareness of this disorder a high priority. Conversely, nonatherosclerotic artery diseases represent a heterogeneous group of uncommon conditions (nonatherosclerotic PAD [NAPADs]) that can cause arterial ischemia may have PAD; however, it is important to differentiate between PAD and NAPAD. Given the uncommon nature of NAPAD, the differential diagnosis is unfamiliar to most clinicians. PAD is the most common arterial cause of lower-extremity symptoms and therefore must be considered the leading diagnosis. Clues suggesting that symptoms are due to PAD include the appropriate patient age, the presence of associated cardiovascular risk factors (diabetes mellitus, tobacco abuse, hypercholesterolemia, hypertension), clinical manifestations of atherosclerosis in other vascular beds (myocardial infarction, ischemic stroke), characteristic physical findings, and a typical appearance on imaging studies. Leg discomfort in patients with PAD as described by the Rose criteria is a deep, cramp-like achiness in muscle groups during effort resulting from exercise-induced fatigue, discomfort, or pain that occurs in specific limb artery, cool or atrophic skin, and nail changes. Elevation pallor, dependent rubor, skin ulcerations, and symmetrical ischemic neuropathy are more typical of advanced cases of PAD. Normal pulses do not exclude the presence of PAD. The angiographic pattern of atherosclerotic PAD is characterized by vessel wall calcification, multivessel involvement, a mixture of focal and diffuse lesions, and association with typical ostial and proximal artery locations. A constellation of patient history, physical examination findings, and the results of specific diagnostic tests may prompt the suspicion for NAPAD. Examples include a competitive cyclist who notes leg fatigue with extreme exertion (iliac artery endofibrosis) or a high school soccer player who can no longer compete because of severe limb discomfort (popliteal entrapment syndrome). Lack of awareness of these alternative diagnoses may delay appropriate treatment and result in progressive disability. The clues to discern between PAD and NAPAD are highlighted in Table 1. A diagnostic approach to patients with leg pain with exertion is presented in Figure 2.

**Nonatherosclerotic Arterial Causes of Lower-Limb Discomfort**

Intermittent claudication (IC) is defined as reproducible fatigue, discomfort, or pain that occurs in specific limb muscle groups during effort resulting from exercise-induced ischemia. Atherosclerosis is by far the most common cause of IC, and it is much more common in the lower extremity than the upper extremity. Nonatherosclerotic causes of leg discomfort can be divided into vascular and nonvascular conditions (Table 2). Although the minority of patients with IC provide a classic history of calf muscle tightness with walking that is promptly relieved by stopping the activity and resting, a nonatherosclerotic origin for IC should be suspected in patients who are young, have no other manifesta-
tions of atherosclerosis, and who have a paucity of athero-
sclerotic risk factors. Additionally, when a patient presents
with a condition known to cause nonatherosclerotic IC (ie,
thromboangiitis obliterans [TAO]), lower-extremity arterial
involvement should be actively considered. Furthermore, in
cases when there is a discrepancy between symptoms and
imaging, the possibility of an alternative diagnosis other than
atherosclerosis should be entertained. Here, we review the
specific unique manifestations of popliteal artery entrapment,
cystic adventitial disease (CAD) of the popliteal artery,
edofibrosis of the iliac artery, fibromuscular dysplasia
(FMD), arteritis, idiopathic midaortic syndrome, and TAO, all
representing vascular, nonatherosclerotic causes of IC. Features
of these conditions are summarized in Tables 3 and 4.

Popliteal Artery Entrapment Syndrome
Popliteal artery entrapment syndrome (PAES) results from
pressure exerted on the popliteal artery by muscles or
ligaments within or surrounding the popliteal fossa.14 There
are 6 types of PAES, largely determined by the structures that
entrap the artery (types I–IV; Figure 315). Rarely, the vein is
also involved (type V). A sixth type has been described in
which the symptoms are functional, a result of a hypertro-
phied medial head of the gastrocnemius muscle (type VI).16
Symptoms of PAES range from pain, paresthesias, and cold
feet after exercise to ischemic rest pain and tissue necrosis.
A recent review of the published literature regarding PAES
found IC to be the most common presenting symptom.17
Progressive limb ischemia is an uncommon presentation and
more typical of undiagnosed cases in which arterial degener-
ation and poststenotic aneurysmal dilatation with emboliza-
tion occur. In longstanding cases, well-developed arterial
collaterals may actually result in milder symptoms. Bilateral
symptoms have been described, prompting the need for
investigation of both limbs regardless of whether symptoms
are unilateral or bilateral.17,18 Entrapment of the popliteal vein
results in leg swelling, heaviness, varicosities, nocturnal calf
cramping, and even deep vein thrombosis.19

Findings of anatomic entrapment are not uncommon. In 1
postmortem study, anatomic abnormalities of the popliteal
fossa were found in 3 of 86 subjects (3.5%).20 Ultrasono-
graphic evidence for popliteal artery occlusion with provoc-
active maneuvers has been described in as many of 80% of
tested asymptomatic individuals.17 Clinically evident PAES
is rare, described in as few as 33 of 20 000 (0.165%) Greek
military recruits.21 Nonetheless, it is a cause of disabling limb
symptoms in young individuals presenting with IC, often
described more in men than in women.18

The diagnosis of PAES is suggested by demonstration of
popliteal artery compression on active pedal plantar flexion
against resistance. This is manifested by a decrease in the
intensity of the pulse examination or with loss of the
continuous-wave Doppler signal during provocative maneu-
vers while a probe is placed over the distal tibial arteries.
Pulse-volume recordings and segmental pressures should be
measured at rest with the knee extended and the ankle in the
neutral, dorsiflexed, and plantarflexed positions. Exercise
treadmill studies may also be helpful by demonstrating
diminished limb arterial pressure after exercise in the symp-
tomatic limb. Arterial duplex ultrasonography may demon-
strate abnormalities when performed in these provocative
positions.22 In a series of 16 healthy volunteers, popliteal

Figure 1. Examples of various types of lower-extremity peripheral artery dis-
ease. A, Halo sign caused by artery wall edema, typical of vasculitis. B, Com-
piled tomographic angiography reconstruction of lower extremities revealing
diffuse arterial calcification, typical of atherosclerosis. C, Angiography reveal-
ing transient occlusion of the popliteal artery on active plantar flexion (right),
consistent with popliteal artery entrap-
ment. D, Typical beaded appearance of
the medial fibroplasia type of fibromuscu-
lar dysplasia (FMD) in the right exter-
nal iliac artery. Note the associated an-
eurysms of the common iliac arteries,
potentially representing aneurysms asso-
ciated with FMD or combined athero-
sclerosis and FMD.
Table 1. When to Suspect Nonatherosclerotic Peripheral Artery Disease in a Patient With Lower-Extremity Symptoms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claudication characteristics</td>
<td>Most patients with claudication caused by PAD present with reproducible symptoms</td>
</tr>
<tr>
<td>Claudication symptoms from atherosclerosis</td>
<td>Typically resolve within several minutes of stopping activity, and occur after a fixed amount of exertion</td>
</tr>
<tr>
<td>Symptoms typically occur sooner on an incline</td>
<td></td>
</tr>
<tr>
<td>Symptoms only during extreme exertion are not typical of PAD</td>
<td></td>
</tr>
<tr>
<td>Age &lt;50 y</td>
<td>PAD prevalence rises with age and is less common before 50 y of age</td>
</tr>
<tr>
<td>Lack of cardiovascular risk factors</td>
<td>PAD is a marker of systemic atherosclerosis</td>
</tr>
<tr>
<td>Tobacco abuse and diabetes mellitus represent the strongest risk factors for PAD</td>
<td></td>
</tr>
<tr>
<td>Sudden onset, rapid progression, or waxing and waning pattern</td>
<td>Claudication symptoms from atherosclerosis are typically stable over time</td>
</tr>
<tr>
<td>An exception is acute limb ischemia resulting from systemic embolism</td>
<td></td>
</tr>
<tr>
<td>Associated symptoms</td>
<td>Symptoms associated with NAPAD include fever, malaise, weight loss, upper-extremity claudication, atypical ulcerations, rash suspicious for systemic vasculitis, and superficial venous thrombosis</td>
</tr>
<tr>
<td>Elevated inflammatory markers or hematologic abnormalities are more typical of NAPAD</td>
<td></td>
</tr>
<tr>
<td>Known systemic illness that may cause NAPAD</td>
<td>If a patient with lower-extremity symptoms has a known diagnosis of a potential cause of NAPAD (eg, FMD), lower-extremity involvement should be entertained</td>
</tr>
<tr>
<td>Physical findings not typical for atherosclerosis</td>
<td>The Allen’s test is abnormal</td>
</tr>
<tr>
<td>Pedal pulse intensity is affected by knee flexion</td>
<td></td>
</tr>
<tr>
<td>A discrepancy in brachial artery blood pressure or radial-femoral pulse delay exists in a young patient</td>
<td></td>
</tr>
<tr>
<td>There is evidence of isolated distal arterial disease</td>
<td></td>
</tr>
<tr>
<td>Imaging findings atypical of atherosclerosis</td>
<td>Atheroendothelial lesions are typically variable in length and associated with arterial calcifications</td>
</tr>
<tr>
<td>Atheroendothelial lesions are usually present in several vascular beds such as the coronary, cerebrovascular, renal, and aorta</td>
<td></td>
</tr>
</tbody>
</table>
| Atheroendothelial lesions are most often ostial/proximal in location | PAD indicates peripheral artery disease; NAPAD, nonatherosclerotic PAD; and FMD, fibromuscular dysplasia.

artery compression was demonstrated in 84% of limbs on active plantar flexion,23 highlighting the potential for false-positive results. For this reason, dynamic computerized tomographic arteriography or magnetic resonance arteriography may be helpful to confirm the diagnosis. Computerized tomographic arteriography and magnetic resonance arteriography also demonstrate the causative structures resulting in entrapment of the vascular structures. Data on the utility of these tests are limited to small series.74

Treatment of PAES types I through V is by surgical relief of the entrapment by resection or translocation of the compressing elements. In the case of functional PAES (type VI), part of the medial head of the gastrocnemius muscle is resected or translocated to relieve pressure on the vascular structures.16 Prompt therapy should be offered because of the progressive nature of the disorder. If the disease is advanced, arterial reconstruction or surgical bypass of an occlusion or aneurysm, preferably with a venous autologous graft, may be required.

Cystic Adventitial Disease (CAD) of the Lower-Extremity Arteries

Cystic adventitial disease (CAD) is a rare cause of IC, typically found in middle-aged men and affecting mainly the popliteal artery.25 Bilateral disease has been described,26 as has CAD in other locations such as the external iliac, femoral,27 radial, or ulnar arteries.26 Symptoms are caused by compression of the arterial lumen by a cystic collection of mucinous material inside the adventitia of the artery.28 Various theories have been proposed for the origin of CAD, including a systemic disorder, repetitive trauma, and a persistent embryonic synovial track.29

Classically, limb pain will linger for as long as 20 minutes on cessation of activity, as opposed to the rapid relief that most patients with PAD-associated limb discomfort experience. CAD-related IC may wax and wane or even disappear for as long as several months, just to reappear without any clear inciting event.30 Acute limb ischemia secondary to arterial compression and thrombosis has also been described.31 The diagnosis is suspected when pedal pulses disappear with passive knee flexion (Ishikawa sign)26 and occasionally with exercise25 and is confirmed with imaging, typically magnetic resonance imaging.33 Conventional angiography may not represent the gold standard diagnostic modality for CAD in that it may only demonstrate compression of the arterial lumen (hourglass sign or scimitar sign) without further characterization of the underlying origin.25

There are no uniform recommendations for the treatment of CAD. Image-guided aspiration, surgical resection followed by autologous venous interposition graft, and adventitial resection have been described.29,32 Percutaneous transluminal angioplasty has not been found to be useful. Data on long-term surveillance are lacking; however, recurrence is possible, thereby prompting the need for prospective surveillance.52

Endofibrosis of the Iliac Artery

Endofibrosis of the iliac artery is a rare cause of arterial stenosis, reported most often in highly functioning and competitive cyclists34 and highly functioning runners.35 It is thought to result from repetitive trauma, predominantly of the external iliac artery. Symptoms include IC and a sensation of swelling or paresthesia in the proximal lower limb at the time of maximal exertion.36 Physical examination may be normal at rest, although a bruit may be heard over the ipsilateral pelvic fossa or inguinal region.37 Diagnostic imaging should include pre-exercise and postexercise ankle pressure determination with maximal, symptom-limiting treadmill exercise. Further imaging with duplex ultrasonography and contrast angiography,36 preferably when the leg is flexed at the hip in the cycling position, will reveal concentric stenosis and often lengthening of the affected iliac artery. Intravascular ultrasound has been reported to aid in the diagnosis, in addition to
intra-arterial translesional pressure gradients. Although no large-scale trials exist to guide treatment, most report surgical revascularization with patch angioplasty or interposition grafts. More recently, endovascular therapy with percutaneous transluminal angioplasty and stent deployment have demonstrated efficacy.35

Fibromuscular Dysplasia

FMD is a noninflammatory, nonatherosclerotic arterial disease38 that occurs most commonly in women 20 to 60 years of age. FMD has been described in men, children, and the elderly.39 The true prevalence of FMD is unknown; however, in a series of potential renal donors40 and from incidental findings on imaging, it is not rare.41 The clinical manifestations of FMD depend on its arterial distribution. The renal arteries are affected in 75% and the extracranial carotid arteries in 70% of patients with FMD.38,42 FMD may be asymptomatic and incidentally discovered when imaging is performed for other reasons.

Although less common, FMD may affect the iliac,43 femoral, or popliteal arteries. Lower-extremity involvement may result in IC, microemboli, or (rarely) critical limb ischemia via dissection or rupture of the artery.22,44 FMD is divided into several types according to which arterial layer is affected and by the arteriographic pattern of disease: medial fibroplasia, intimal fibroplasia, and adventitial (periarterial) hyperplasia. Medial fibroplasia is the most common type, making up 80% to 90% of cases in the renal arteries. It is characterized by intra-arterial fibrotic webs that give rise to a beaded appearance on imaging studies in which the beads are larger than the lumen of the artery. Thus, the diagnosis relies on a combination of clinical and imaging findings. Duplex ultrasonography, magnetic resonance arteriography, and computerized tomographic arteriography can all identify FMD and assess aneurysm formation, but none is as accurate as angiography45 or intravascular ultrasonography.46 The scope of imaging should accommodate the fact that FMD may involve several vascular beds. Thus, patients with extracranial FMD should be screened for intracranial aneurysms and for renal involvement, especially if they are hypertensive.47 The differential diagnosis of FMD includes atherosclerosis, systemic vasculitis, segmental arterial mediolysis,48 and arterial aneurysms and dissections from other causes (eg, genetic collagen disorders). It should be noted that in older individuals FMD and atherosclerosis may occur simultaneously (see Figure 1). Treatment of FMD depends on the presentation and extent of arterial involvement. Asymptomatic patients are usually empirically prescribed aspirin. Despite a lack of high-quality data, relying on experience from treatment of renal arteries and on case reports on the iliac arteries49 in which percutaneous transluminal angioplasty has proved to be successful in patients with FMD,50 it is recommended as first-line therapy for patients with debilitating symptoms related to lower-extremity artery involvement. Of the 10 case reports in the literature on spontaneous iliac artery dissection in

Table 2. Differential Diagnosis of Intermittent Claudication

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>Popliteal artery entrapment syndrome</td>
</tr>
<tr>
<td>Cystic adventitial disease of the popliteal artery</td>
<td>Iliac artery entodistosis</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
<td>Venous claudication</td>
</tr>
<tr>
<td>Large- and medium-vessel vasculitis</td>
<td>Nonvascular</td>
</tr>
<tr>
<td>Chronic exertional compartment syndrome</td>
<td>Arthritis (lumbosacral spine, hip or knee)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Hamstring muscle tightness</td>
</tr>
<tr>
<td>Symptomatic popliteal (Baker) cyst</td>
<td>Plantar fasciitis</td>
</tr>
</tbody>
</table>

Figure 2. Diagnostic approach to patients with leg pain with exertion. NAPAD indicates nonatherosclerotic peripheral artery disease; PVR, pulse-volume recording; DUS, duplex ultrasonography; CTA, computed tomographic angiography; and MRA, magnetic resonance angiography.
patients with FMD, all patients were treated surgically with prosthetic or vein graft.44

**Medium- and Large-Vessel Vasculitis**

Several large- and medium-vessel vasculitides have been described to affect the lower extremities. These include Takayasu arteritis (TA), giant-cell arteritis (GCA), and Behçet disease. TA is a large-vessel vasculitis that typically, but not exclusively, affects young women of Asian or Latin descent.51 An analysis of a large nationwide database in the United Kingdom revealed a prevalence of 0.8 per 1 million population, significantly lower than the reported incidence of 3.5 per 1 million in Japan.52 Criteria for the diagnosis of TA include young age, claudication of >1 extremity (classically an upper extremity), a diminished brachial pulse, asystolic blood pressure difference of >10 mm Hg between the brachial arteries, a bruit over at least 1 subclavian artery, and imaging evidence of long segments of tapering stenosis of the aorta or one of its large branches.53 In contrast to PAD, IC resulting from TA is much more common in the upper extremity than the lower extremity.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Atherosclerosis</th>
<th>Popliteal Entrapment</th>
<th>Cystic Adenovitlial Disease</th>
<th>Large- and Medium-Vessel Vasculitis</th>
<th>Midaortic Syndrome</th>
<th>Endofibrosis</th>
<th>FMD</th>
<th>Buerger Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Typically &gt;50 y</td>
<td>Teenagers and young adults</td>
<td>4th–5th decade</td>
<td>2 Peaks: young adults (Takayasu/Behcet) and elderly (giant-cell arteritis)</td>
<td>Children and young adults</td>
<td>Young, physically active adults</td>
<td>Variable presentation</td>
<td>Typically &lt;50 y</td>
</tr>
<tr>
<td>Sex predominance</td>
<td>Male&gt;female</td>
<td>None</td>
<td>Male&gt;female</td>
<td>Female&gt;male in Takayasu</td>
<td>Insufficient data</td>
<td>None</td>
<td>Female&gt;male</td>
<td>Male&gt;female</td>
</tr>
<tr>
<td>Symptom trigger</td>
<td>Reproducible, often stable over time; walking on incline produces earlier symptoms</td>
<td>Exercise is a typical trigger</td>
<td>Variable onset, may wax and wane</td>
<td>Symptoms may exacerbate with active vasculitis and abate with treatment or become chronic in the fibrotic stage of disease</td>
<td>Claudication is rare; the severity of aortic narrowing dictates symptom severity</td>
<td>Often extremely strenuous activity</td>
<td>Variable</td>
<td>Often constant</td>
</tr>
<tr>
<td>Time to symptom resolution on rest</td>
<td>Several minutes unless critical limb ischemia in which case rest pain may be persistent, particularly at night</td>
<td>Several minutes unless rest pain and tissue necrosis develop in neglected cases</td>
<td>Up to 20 min</td>
<td>Symptoms may be constant or resolve after several minutes as in atherosclerosis</td>
<td>Symptoms may be constant or resolve after several minutes as in atherosclerosis</td>
<td>Symptoms resolve after activity</td>
<td>Symptoms may be constant or resolve after several minutes</td>
<td>Symptoms may be constant or resolve after several minutes</td>
</tr>
<tr>
<td>Additional symptoms</td>
<td>Other vascular beds typically affected, specifically coronary and cerebral</td>
<td>None</td>
<td>None</td>
<td>Fever, night sweats, weight loss, malaise, arthralgia, renal failure, hematologic abnormalities, TIA/CVA; oral or genital ulcerations and uveitis suggest Behcet</td>
<td>Hypertension in a child or teen is the most common presenting symptoms</td>
<td>None</td>
<td>Extracranial carotid artery and renal circulation is typical</td>
<td>Superficial vein thrombosis, tissue necrosis</td>
</tr>
<tr>
<td>Other clinical clues</td>
<td>Atherosclerotic risk factors and specifically tobacco abuse</td>
<td>None</td>
<td>None</td>
<td>Asian or Latin descent</td>
<td>None</td>
<td>History of competitive sports, often cycling</td>
<td>None</td>
<td>Tobacco or marijuana abuse</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Diminished pulses, bruits, elevation palp and dependent rubor; in critical limb ischemia, nonhealing ulcers over bony prominences or distal aspects of toes</td>
<td>Popliteal pulse diminished with forced plantar flexion</td>
<td>Popliteal and distal pulses disappear with knee flexion (Ishikawa sign)</td>
<td>Diminished brachial or radial pulse; bruit over the subclavian, carotid, mesenteric or renal arteries; pulse delay between the radial and femoral arteries</td>
<td>Pulse delay between the radial and femoral arteries</td>
<td>Can be normal; may hear bruit in ipsilateral pelvis after activity</td>
<td>Can be normal; may be heard over the femoral artery and over the carotid and renal arteries</td>
<td>Tobacco staine, digital ischemia, abnormal Allen test</td>
</tr>
<tr>
<td>Treatment</td>
<td>Atherosclerosis risk factor modification, consider endovascular and surgical treatment</td>
<td>Early surgical repair of anatomic abnormality preferred</td>
<td>Aspiration or resection of cysts</td>
<td>Immunomodulating agents; endovascular and surgical treatments are reserved for complications</td>
<td>Surgery is most common; endovascular approach advocated as bridge</td>
<td>Surgical bypass; endovascular repair has been described</td>
<td>Antiplatelets; endovascular or surgical approach for complications</td>
<td>Avoidance of tobacco and nicotine products</td>
</tr>
</tbody>
</table>

FMD indicates fibromuscular dysplasia; TIA/CVA, transient ischemic attack/cerebrovascular accident.
GCA, a granulomatous arteritis of medium- and large-sized arteries, represents a component of a spectrum of arteritides along with TA.54 It is a disease of adults >50 years of age. Its prevalence is estimated to be 15 to 33 per 100,000 population.55 It is characterized by new-onset headache, scalp tenderness, jaw claudication, and in advanced cases, visual disturbance.56 Lower-extremity involvement has been described in GCA.54 Although typically affecting the aortic arch and the great vessels, TA may also result in a midaortic variant. This variant causes abdominal aortic coarctation, resulting in renovascular hypertension, IC, or both.57 In an analysis of 58 patients with this variant of TA and renovascular hypertension in India, it has been found to be equally common in men and women.58 In a retrospective analysis of 272 patients with TA spanning 50 years, 41 (≈15%) were found to have IC.59

Finally, Behcet disease is a multisystem vasculitis that affects both arteries and veins. When present, large-artery involvement is the most typical and may result in both aneurysmal dilatation and, less commonly, stenosis or artery occlusion.60 Lower-extremity involvement has also been described in the iliac, femoral, popliteal, and posterior tibial arteries.61,62 Isolated infrainguinal involvement is distinctly unusual.

Table 4. Comparison of Imaging and Laboratory Characteristics of Lower-Extremity Atherosclerosis and Nonatherosclerotic Peripheral Artery Disease

<table>
<thead>
<tr>
<th>Imaging characteristics</th>
<th>Atherosclerosis</th>
<th>Popliteal Entrapment</th>
<th>Cystic Adventitial Disease</th>
<th>Large- and Medium-Vessel Vasculitis</th>
<th>Midaortic Syndrome</th>
<th>Endofibrosis</th>
<th>FMD</th>
<th>Buerger Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive imaging</td>
<td>Physiologic testing should be performed at rest and with exercise; on DUS, there is varied lesion lengths from to diffuse; lesions associated with calcification</td>
<td>Physiologic testing should be performed at rest and with exercise; on DUS, there is varied lesion lengths from to diffuse; lesions associated with calcification</td>
<td>None</td>
<td>Periarterial edema (halo sign)</td>
<td>Reduced ABI</td>
<td>Physiological testing should be performed after intense activity (eg, running, cycling)</td>
<td>Arterial beading may be seen in the distal renal or distal extracranial carotid arteries</td>
<td>Asymmetrical digital waveforms</td>
</tr>
<tr>
<td>CTA/MR</td>
<td>Multiple vascular bed involvement, varied lesion lengths, calcifications, irregular plaque</td>
<td>Studies in the neutral position, flexion, and extension are necessary for the diagnosis</td>
<td>MR may show adventitial fluid collections that can appear to be confluent with the synovium</td>
<td>Long segments of arterial narrowing (macaroni sign), typical distribution; arthritis may be identified</td>
<td>Abdominal aortic narrowing</td>
<td>Redundant external iliac arteries</td>
<td>Arterial beading may be visualized</td>
<td>Atherosclerosis may also be present</td>
</tr>
<tr>
<td>Angiography</td>
<td>As CTA/MR</td>
<td>Runoff may disappear with plantar flexion</td>
<td>Not the modality of choice; hourglass or stenotic signs</td>
<td>Long segments of arterial narrowing in a typical distribution</td>
<td>Variable infraaortic aortic narrowing; renal artery occlusion</td>
<td>As CTA/MR</td>
<td>As CTA/MR</td>
<td>Abnormal palmar arch, corkscrew collaterals</td>
</tr>
<tr>
<td>Distribution</td>
<td>Multiple vascular beds</td>
<td>Isolated to the popliteal fossa</td>
<td>Most commonly isolated to the popliteal fossa but can appear in other locations</td>
<td>Aortic arch and great vessels or midaortic syndrome (Takayasu); temporal arteries</td>
<td>Abdominal aorta</td>
<td>External iliac arteries</td>
<td>Most common in the renal and extracranial carotid artery distribution</td>
<td>Distal disease precedes proximal disease</td>
</tr>
</tbody>
</table>

| Laboratory characteristics | Elevated inflammatory markers | Not typical | Not typical | Not typical | Typical, but not essential during active phase | Not typical in the idiopathic form | Not typical | Not typical | Not typical |

FMD indicates fibromuscular dysplasia; DUS, duplex ultrasound; ABI, ankle brachial index; CTA, computed tomographic angiography; and MR, magnetic resonance.

Figure 1).55,66 Long segments of smooth narrowing or aneurysmal dilatation may be visualized with computerized tomographic arteriography or magnetic resonance angiography.67 Additional testing with positron emission tomography to demonstrate uptake of fluorodeoxy-D-glucose in the arterial wall may prompt the diagnosis even before visible anatomic arterial changes occur. However, uptake may remain visible long after treatment has been initiated,68 and 2 small studies comparing positron emission tomographic computed tomography with clinical and laboratory assessment of disease activity have yielded conflicting results.69,70

Treatment of vasculitides includes managing inflammation and treating arterial complications (ie, stenosis, occlusion, aneurysm).60,71 While the disease is active, IC may respond to treatment with antiinflammatory agents, including corticosteroids, methotrexate, azathioprine, and cyclophosphamide. The effects of tocilizumab, an interleukin-6 inhibitor, have not been described specifically for the treatment of lower-extremity ischemia associated with GCA, although it has been used in the treatment of both TA and GCA.72 In contrast, in the fibrotic stages of the disease, endovascular or surgical intervention may be necessary to correct the underlying obstruction to flow or to exclude aneurysms.73 Surgical options in TA include aortolocic and aortofemoral bypass.59,73 Aneurysm repair in patients with Behcet disease has been complicated by disease recurrence despite antiinflammatory treatment in 2 retrospective series.62,74
Idiopathic Midaortic Syndrome

Midaortic syndrome refers to narrowing of the subisthmic aorta. It is a form of aortic coarctation most probably arising from an embryonic developmental disorder. This should be differentiated from involvement of the abdominal aorta in large-vessel vasculitis. The diagnosis is commonly made in children and young adults. It can affect the suprarenal, renal, or infrarenal segments of the abdominal aorta. Involvement of the renal artery origins is typical and may result in renovascular hypertension. IC has been described, albeit rarely. In a retrospective series of a mixed population of 16 patients with idiopathic and secondary midaortic syndrome, 2 presented with IC. In another retrospective series of 17 patients, most of whom did not have elevated inflammatory markers, only 3 had lower-extremity symptoms, although in 4 patients a substantial blood pressure gradient could be measured between the arms and the legs. Treatment of midaortic syndrome has classically been surgery. Recurrence with percutaneous transluminal angioplasty is said to be high owing to extensive aortic involvement and significant elastic recoil and has been proposed as a bridge to surgery. High-radial-strength balloon-expandable stents, either bare or covered with a fabric material, may represent an effective primary modality for therapy.

TAO (Buerger Disease)

TAO is a segmental inflammatory condition that affects small and medium arteries, veins, and nerves. TAO is a disease of young people, typically <50 years of age, who abuse tobacco, most classically in the form of cigarettes. Atherosclerotic risk factors other than smoking are commonly absent. Clinical manifestations of TAO include pain in a digit or extremity, digital ischemia, Raynaud phenomenon, distal digital ulcerations, and extremity claudication. As TAO progresses, it may progress to extremity gangrene and amputation. TAO is a clinical diagnosis. Commonly, >2 extremities are involved, sometimes subclinically, wherein patients without obvious upper-extremity involvement have an abnormal Allen test. In a retrospective series of 112 patients, 61 (72%) had lower-extremity ischemic ulcerations. Physical examination must include a thorough vascular examination with particular attention to pulses, bruits, and assessment of the ankle brachial index. An Allen test should be performed to demonstrate arterial involvement of the upper extremity even if asymptomatic. Markers of inflammation and autoantibodies are usually absent and are assayed to exclude alternative diagnoses. Anti-endothelial antibodies, not routinely measured, have been described in Buerger disease. Imaging studies should be used to identify the distribution of vascular involvement when TAO is suspected, demonstrating normal proximal arteries. Proximal sources of emboli should be excluded, typically with transthoracic and transesophageal echocardiography. Although computerized tomographic arteriography and magnetic resonance arteriography may be helpful in excluding atherosclerosis, diagnostic arteriography is often needed to demonstrate the distal in-
volvement of arteries and the usual absence of atherosclerotic lesions. A typical presentation is that of segmental arterial occlusion and corkscrew collaterals (Martorell sign). However, contrary to popular belief, corkscrew collaterals are not pathognomonic for TAO. Biopsy, usually reserved for atypical cases, demonstrates a highly cellular thrombus with relative sparing of the vessel walls. Features distinguishing it from atherosclerosis include disease distribution, involvement of both the upper and lower extremities, associated superficial venous thrombosis, a paucity of atherosclerotic risk factors, and normal proximal large arteries.

The cornerstone of treatment is tobacco cessation. Complete abstinence is crucial because a reduction in tobacco exposure does not prevent progressive tissue necrosis and limb loss. Tobacco cessation has been supplemented by various adjuvant therapies. Intravenous alprostadil, a stable prostacyclin analog, has been compared with aspirin in a prospective, double-blind, randomized trial of 133 subjects with TAO and critical limb ischemia. Fifty-eight of the 68 patients (85%) who received alprostadil showed response to treatment as measured by ulcer healing and pain reduction compared with 11 of 65 patients (17%) who received aspirin alone at 21 to 28 days (P<0.05). Another prospective, double-blind, randomized, placebo-controlled trial examined the effect of 2 doses of oral iloprost on ulcer healing, pain, and amputation-free survival in 319 patients with TAO. Patients were treated for 8 weeks and followed up for 6 months. Only patients receiving low-dose iloprost experienced greater pain relief (63% versus 49%; P=0.02). Other vasodilators such as calcium channel antagonists, peripheral α-blockade, and sildenafil have not been formally evaluated in TAO. The results of surgical venous bypass grafts for the treatment of TAO-related lower-extremity ischemia have been reported. In a retrospective study of 71 venous graft bypass procedures in 61 patients, of whom 38 also underwent sympathectomy, the mean follow-up was 62.6 months. There were 14 early failures and 24 late failures, and the primary, assisted primary, and secondary patency rates at 5 years were 48%, 58%, and 62.5% and at 10 years were 43%, 52.1%, and 56.3%, respectively. Other treatments that have been attempted include bosentan, spinal cord stimulation, and intermittent pneumatic compression. In a pilot study, vascular endothelial growth factor was injected intramuscularly into 7 limbs of patients with critical limb ischemia who also fulfilled the diagnostic criteria for TAO, resulting in ulcer healing in 5 and resolution of rest pain in 2. Imaging studies revealed improved collateral blood flow in all treated legs. Finally, lumbar sympathectomy and periartrial sympathectomy have also been described with various degrees of success.

Conclusions

The most common vascular cause for exertional limb discomfort is PAD resulting from atherosclerosis. However, alternative diagnoses must be considered for patients without the classic risk factors for atherosclerosis and those without evidence of atherosclerosis involving other vascular beds. NAPAD can be caused by extrinsic arterial compression (PAES), abnormalities in the artery wall (CAD, FMD), inflammatory states (TA), and tobacco-related disorders (TAO). A thorough understanding of these disorders will allow prompt and appropriate diagnosis and treatment. The practicing cardiovascular specialist must have a high index of suspicion for these diagnoses.

Disclosures

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