

ROBERT

Hi, I'm Rob McBane, and I'm here today with Dr. Leslie Cooper. And we're going to talk to you today about

MCBANE:

claudication, a topic that's really near and dear to our hearts. Neither one of us have any disclosures to make this morning.

So for the next 20 minutes or so, I would like the learner to consider these objectives. I think that we should talk about the natural history of peripheral arterial occlusive disease. I think the learner should be able to understand the treatment strategies and to know how to assess intermittent claudication. It's important to discern atypical presentations of the disease and disease mimickers.

I think it's always important to start with a case so that we can hang this diagnosis on a real live individual. This is a patient that I saw three years ago, and I just had the opportunity to see her back a couple of weeks ago. She's an 84-year-old, vibrant female from our community. And three years ago, she noted the onset of right calf discomfort with walking. Very typical presentation.

Her symptoms would reproducibly occur at 30 yards of walking, and after about a block, she had to stop walking because the pain became so intense. She would then stand there for five minutes or so and her symptoms would be completely resolved. It's important to note that she had no rest pain or ulcerations limiting her.

Now her past medical history was important for cardiovascular risk. She had been a prior smoker, but was able to stop. Currently, she has a history of hypertension and hyperlipidemia, and unfortunately, is not on medications for either of these diagnoses.

Her physical exam was relevant for high blood pressure, which was present in both arms in a symmetric fashion. Why do I say symmetric? Because in patients with peripheral arterial occlusive disease, oftentimes they can have a reduced blood pressure, typically in the left upper extremity, which is an important marker for subclavian arterial occlusive disease, but that was absent in this patient. Her cardiac examination, including a careful auscultation of her carotid arteries, was normal, and specifically, there was no carotid bruits.

Refer next to her vascular examination. Her upper extremity pulse examination was completely normal. At Mayo Clinic, we grade a normal pulse as a 4, and anything less than 4 is considered abnormal. A 5 would be aneurysmal disease. On the upper of the two numbers is the right lower extremity. And the lower of the two is the left.

And so you can see that on the right lower extremity, there was a reduced femoral pulse with an absent right popliteal posterior tibial and dorsalis pedis pulse in that limb. On the left the pulses were normal. Specific evaluation of her feet is relevant for anybody with intermittent claudication. And you can see that she has no ulcers, she had no rubor, no fissures, and specifically, there was no lower extremity edema.

This set of testing was obtained prior to my visit with the patient. This is the vascular laboratory assessment that we do in the vascular center. This is the physiologic testing that everybody should do in any patient with lower extremity arterial symptoms. Up in the left-hand corner, the upper left corner, you can see the Doppler signals. Triphasic or biphasic responses would be considered normal. And you can see that at the superficial femoral popliteal and lower blood-- lower arterial segments in her right lower extremity that these signals were abnormal, consistent with a flow limiting lesion. On the right, or sorry, on the left, for the most part the Doppler signals are normal.

In the upper right corner is the ankle-brachial index data. In UNI, or patients with normal lower extremity arterial perfusion, a normal ankle-brachial index should be somewhere between 1 and 1.2. Anything less than 0.5 would be considered severe. So you can see for the right lower extremity, this patient had severely reduced ankle-brachial indices.

In the left lower portion of this lab, you can see the exercise data. And just as we told her, or just as she told us, the distance to the onset of symptoms was a very reproducible 34 yards. Despite encouragement from our vascular laboratory technicians, the patient was not able to walk for more than 140 yards because of disabling claudication. Following the exercise, we repeat the ankle-brachial indices, and you can see that at 1 minute post-exercise, the right pedal ankle-brachial index was not obtainable because of such severe disease in that limb. And so in summary, this patient has severe right and only modest left lower extremity arterial occlusive disease.

A CT angiogram with runoff was also obtained prior to my visit. Here are three such panels showing the proximal vasculature and the vasculature below the knee on the far right. You can see that this individual has a complete occlusion of the superficial femoral artery, however, this is a short segment occlusion. The blood vessels reconstitute below this occlusion, and the patient has actually fairly decent blood flow to her right foot.

So what is the natural history of this patient? If we were to take a population of patients with peripheral arterial occlusive disease over the age of 55, by far most of these individuals would have asymptomatic disease. 50% would present with asymptomatic leg lower extremities. 40% would have a symptom of intermittent claudication much like our patient had. And 10% would present with critical limb ischemia.

The natural history can be divided then into peripheral artery outcomes and morbidity and mortality outcomes. So at five years, the peripheral arterial outcomes are actually quite stable with 75% of patients being either no better nor any worse compared to their presenting symptoms. About 1% per year would require an intervention, such as a bypass surgery. And about 1% per year would require an amputation. The big deal with regards to peripheral arterial occlusive disease is the risk of mortality. You can see that after five years, a full 30% of individuals will not be alive, and 20% will have suffered either a heart attack or a stroke.

So how relevant is the identification of peripheral arterial occlusive disease? Well, it's very relevant for the very reason that it's so common. Approximately 10 million Americans have PAD, and one million of Americans of these will develop symptoms each year. Now it's important for the slide that I just showed you, which said that the risk of mortality was high, and it turns out that PAD is an independent risk factor for cardiovascular mortality. Moreover, early detection and treatment hopefully will decrease walking impairment, the progression to critical limb ischemia, and amputation.

This slide, taken from the task guidelines, shows the rather dismal survival in patients who have PAD. If they have intermittent claudication, here, defined as IC, you can see that their overall mortality at five years would be 30%, with a 15 year mortality of up to 70%. If they present with critical limb ischemia, these numbers are even worse.

Survival is directly related to ankle-brachial index severity. The more severe your ankle-brachial index is, the worse your outcome is. And this is true across a spectrum of patients, but it's also true in patients who have non-compressible vessels. These are individuals who probably have untreated or poorly treated diabetes mellitus, and you can see that their prognosis is equally severe.

This is largely because of coexisting vascular disease. Several studies have shown that patients with peripheral arterial occlusive disease have a 50% likelihood of having severe either left main disease or three vessel disease. Moreover, these patients have severe carotid disease in a third, and severe renal artery disease in another third. And so co-existing vascular disease takes its toll in these patients.

When you see a patient with intermittent claudication and they have neither rest pain nor ulceration, a very useful treatment is a supervised walking program. We and others use the Canadian Walking Program, which is a program which entices the patient to walk for 30 minutes five days per week. I tell my patients to push it until they have moderate symptoms, and then they stop and rest until their symptoms resolve.

But remember, when you stop and rest, you have to stop the clock. And then you re-initiate the activity. The goal is to walk for 30 minutes in 30 minutes. And when they start, they may indeed take 45 to 60 minutes to complete this 30 minutes of walking.

There is a lot of data supporting a supervised exercise program for the initial treatment of intermittent claudication. Here's an important meta analysis, which reviewed 21 such studies. And you can see that the onset of claudication with the implementation of this exercise program increases by nearly 180%, with a mean increase in claudication distance of 225 yards. Moreover, their maximum distance of walking increases by over 100%, or a mean increase of 400 yards.

Well, how good is walking compared to a more aggressive intervention such as angioplasty and stenting? This was the hypothesis that was tested in the recently published CLEVER trial. In this trial, patients were randomly assigned to either a supervised exercise program, primary stenting, or optimal medical management. And what you can see is that indeed, the supervised walking program beat both the stenting and the optimal medical treatment in the peak walking distance at six months.

This is the newly published PAD guidelines that was just published a couple of months ago. And these guidelines highlight the importance of a supervised exercise program in the initial treatment of PAD. Moreover, the guidelines suggest that patients should be given at least 12 weeks of this walking program before deeming it a failure. And these are both grade 1A indications. For those individuals requiring further interventions, such as a stent or an angioplasty or surgery, the guidelines support the use of those more aggressive interventions, but only after the patient has failed a supervised exercise program.

So when we make the diagnosis of PAD, the first thing that we do is try to stratify patients and try to modify those modifiable risk factors, such as smoking, hypertension, hyperlipidemia, diabetes mellitus. And Dr. Cooper will be talking about that in a moment. If they have lifestyle limiting claudication, we initially begin with an exercise program. If, on the other hand, their presentation is critical limb ischemia or if they failed an exercise program, we then pursue either a CT angiogram or a conventional angiogram to define the anatomy, and then offer the patient revascularization if it's feasible.

The indications for revascularization can be divided into either absolute or relative. The absolute indications, again, are rest pain or non-healing ulceration. The relative indications include lifestyle limiting symptoms.

When thinking about pursuing either an endovascular or a surgical revascularization of your patient's intermittent claudication and peripheral arterial occlusive disease, it's important to think about the five year primary patency rates. These are the data relative to angioplasty and stenting, and where the disease is primarily located. And you can see the higher that you are in the limb, the better the five year primary patency rates. And this is true not only for angioplasty and stenting, but it's also true for bypass grafting.

If you're doing a below knee or a pedal bypass, the best outcomes are with endogenous vein using a saphenous vein as a conduit. You can see that the synthetic grafts, such as PTFE or GORE-TEX, seemed to have a much lower five year primary patency rate. And again, the further that you get down into the leg, the lower the primary patency rates, whether the intervention is an angioplasty and stenting or bypass grafting.

I will now turn the podium over to my colleague, Dr. Cooper, who will discuss medical management of peripheral arterial occlusive disease. Thank you.

**LESLIE
COOPER:**

Good afternoon I'm Leslie Cooper, the Director of the Gonda Vascular Center at the Mayo Clinic. And I'm going to continue the talk today on the management of peripheral arterial disease. I have no disclosures.

A recent meta-analysis of the use of cilostazol for the management of claudication demonstrated that there was a substantial efficacy from 100 milligrams twice daily of cilostazol compared to placebo. This is consistent with the majority of published studies. As Dr. McBane noted in the first part of this talk, the efficacy of a structured, supervised walking program for claudication is considerably better with about a doubling of peak walking time in most studies. For comparison, with cilostazol, the average increase is about a 50% improvement in pain-free and peak walking distance.

There's been renewed interest in the use of statins, not only for the prevention of primary and secondary prevention of cardiovascular events, but also for the management of claudication, the improvement of pain-free and peak walking distances. In early studies from about 11 years ago, simvastatin was demonstrated to improve claudication onset time, as well as pain-free walking distance. These were relatively small studies. The more recent studies published as recently as 2010 demonstrated a somewhat improvement in claudication onset time, but no significant increase in peak walking distance. Statins are still useful, of course, for the prevention of cardiovascular events in patients with established peripheral arterial disease.

A recent finding over the last several years has been a meta-analysis and now a randomized trial looking at the benefit of aspirin for the prevention of cardiovascular events in patients who have no symptoms, but a low ankle-brachial index. In this study from Scotland, over 3,200 patients were randomized, all of whom had an ankle-brachial index of less than 0.9. And as you can see in this event curve, the risk of cardiovascular event in the patients managed with aspirin was about 14% at 10 years.

And this was identical to the rate in placebo treated patients. Therefore, in the current guidelines from the American College of Cardiology and the American Heart Association, the level of recommendation for the use of aspirin in patients with an asymptomatic decrease in ankle-brachial index decrease has gone from a class 1 to now a class 2A recommendation level of evidence C. That is for the use of aspirin in patients who have no symptoms of claudication, but an asymptomatic decrease in ankle-brachial index.

And this is really a shame because there's-- as you can see from this hazard ratio figure, patients who have a decrease in ankle-brachial index actually have a substantially increased risk of total mortality. Unfortunately, today we don't have a great way to intervene to minimize that risk in patients with asymptomatic peripheral arterial disease.

I would also like to highlight two recent trials, both published within the last year. The first, partly from Mayo Clinic, looked at a new phosphodiesterase inhibitor called K-134 for the treatment of claudication in patients with atherosclerosis. And our study demonstrated efficacy similar to that of 100 milligrams twice daily of cilostazol with a very similar side effect profile. In the future, you may see this agent marketed for the management of claudication.

This year in the *Journal of the American Medical Association*, a group from Australia demonstrated significant improvement in pain-free and peak walking distance with the use of ramipril in patients who had claudication. This is a new finding. It's noteworthy because ramipril in the current guidelines is indicated for the management of hypertension. In future guidelines, this may actually be indicated for the management of claudication as well.

To summarize both the data that I've presented and the data from Dr. McBane, exercise is the best treatment for the management of claudication. A structured, supervised treadmill exercise program can improve pain-free and peak walking distance at least 100%, if not more. And many patients, if not most patients, are candidates for an exercise program.

Cilostazol, which is also FDA approved for the management of claudication, has a lesser efficacy, perhaps a 50% improvement, and there are side effects that limit tolerability to about 2/3 of patients. Some people have GI side effects, and others palpitations, which limit the ability to take cilostazol.

Angioplasty has a great efficacy, but unfortunately, only about 10% to 15% of patients have suitable anatomy with the ideal structure for placement of a stent. And finally, surgery, although highly efficacious, is limited by surgical mortality and morbidity, as well as the long-term risk of graft failure. Anatomically, only a minority of patients are suitable candidates for surgery in the setting of intermittent claudication.

To go back to the guidelines, the current 2013 scientific statement and guidelines from the American Heart Association and the American College of Cardiology recommend cilostazol at a dose of 100 milligrams twice daily for the management of claudication with a class 1A indication. Patients who have heart failure are not candidates for cilostazol. For lipid management, there's a class 1A recommendation to treat LDL cholesterol to a level of less than 100 milligrams per deciliter, and a class 2A indication to treat to a level of less than 70 milligrams per deciliter in all PAD patients.

For the management of hypertension, the target is generally less than 140 over 90, or less than 130 over 80 in patients with diabetes or chronic kidney disease. Beta blockers are effective and are, importantly, not contraindicated in patients with peripheral arterial disease. And ACE inhibitors, such as lisinopril, are also very reasonable for the management of hypertension, and as we now see, possibly efficacious for the management of claudication as well.

Aspirin or clopidogrel is indicated to reduce the risk of stroke, myocardial infarction, and vascular death in PAD patients. And for patients with symptomatic disease, it is a class 1A indication. For those patients with asymptomatic decrease in ankle-brachial index, the class of recommendation is 2A level of evidence C.

Finally, it's important to counsel patients who use tobacco products to discontinue tobacco use at every visit. This is a class 1A indication, and assistance with counseling and a plan for quitting is also quite important, highly recommended in the guidelines. Thank you very much.