MANAGEMENT OF CHRONIC ISCHEMIA OF THE LOWER LIMBS

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Contents

Summary

Chronic ischemia of the lower extremities is a disease process, which primarily affects the elderly, and is expected to be increasingly encountered in both the developed and developing world as life expectancies continue to improve in the setting of increasing incidence of contributing risk factors. The purpose of this chapter is to introduce

community health workers, mid-level healthcare providers, and general practitioners to the patient suffering from chronic ischemia of the lower extremity.

1. Introduction

The patient with chronic ischemia arterial insufficiency of the lower extremities may present with a spectrum of symptoms ranging from claudication (effort induced ischemia), rest pain, to tissue loss, with the majority presenting with the former. Claudication infrequently results in limb loss. The associated risk factors however, place the patient at increased risk of myocardial infarction and stroke. Non-operative management is the mainstay of therapy in these patients and includes risk factor modification and close surveillance. For patients with debilitating claudication, rest pain or tissue loss, endovascular and open surgical procedures are the standard treatment modalities for ambulation capacity improvement, and limb loss prevention. For patients who are not candidates for limb salvage, options include would management and amputation.

The purpose of this chapter is to serve as an introduction to the patient with chronic ischemia of the lower limbs, reviewing epidemiology, risk factors, and clinical presentation, diagnostic and therapeutic options. The associated risk factors, which are prevalent in this patient population, affect multiple organ systems (including cardiac, renal, and endocrine systems), emphasis is made on a multidisciplinary approach in the care of patients with chronic ischemia of the lower extremity, calling on the expertise of physicians, wound care specialists, nurses, dieticians, physical therapists, and other professionals.

2. Incidence

The incidence of claudication is directly correlated to age, with 17% prevalence in patients between the ages of 55 to 74. (Fowkes et al, 1991) Symptoms of chronic arterial insufficiency severity vary from asymptomatic to increasingly debilitating forms of claudication, to patients with Critical Limb Ischemia (CLI), which manifests as rest pain, ulceration or gangrene. Patients with CLI are at highest risk of limb loss.

The identification of patients with asymptomatic ischemia allows for risk factor modification, thereby decreasing stroke and cardiovascular morbidity and mortality, while also reducing the risk of progression to critical limb ischemia. The ratio of symptomatic to asymptomatic claudicant patients is approximately one to four. (Norgren et al, 2007) The incidence of symptomatic critical limb ischemia is estimated to be 400 new cases every year per million. (Vascular Surgical Society of Great Britain and Ireland, 1995) For every 100 patients with claudication in the population, one patient per year will develop CLI. The most important risk factors for the development of critical limb ischemia are active smoking, diabetes, and age. (Dormandy et al, 1999)

3. Disease Progression

The risk factors that contribute to the development of chronic ischemia of the lower extremities also affect the vascular beds that supply all the organ systems in the body.

The most clinically apparent effects amongst patients with claudication are on the arteries supplying the heart and brain, with five year follow-up demonstrating a 30% mortality rate, mostly attributed to stroke and myocardial infarction (MI). (Norgren et al, 2007) Studies have shown that up to 90% of patients with Peripheral Arterial Disease (PAD) will have clinically significant Coronary Artery Disease (CAD). (Hertzer et al, 1984) By comparison, on five year follow-up of claudicants, 50-75% of patients will have no change in symptoms or experience symptom improvement. Of the remaining patients, up to 25% will require therapeutic intervention and only 1 - 3.3% will require a major amputation. (Norgren et al, 2007) However, the risk of amputation amongst diabetics with claudication is significantly higher.

Therefore, risk factor modification in claudicants is essential, not only to lower the likelihood of claudication symptom progression, but also to lower the risk of myocardial and stroke related complications. Many of these risk factors function synergistically in increasing the potential for these complications. Medical management includes pharmacotherapy and lifestyle changes, discussed in the following section.

Amongst patients presenting with critical limb ischemia, five year follow-up demonstrate a 50-70% mortality rate, with 35% attributed to cardiovascular deaths. At time of presentation, these patients will likely require an intervention or surgery on their extremity, yet their co-morbidities place them at higher risk for perioperative complications. Postoperatively, they also have an increased one-year mortality rate. Risk stratification is essential in identifying the ideal intervention for these patients, so as to balance the benefits of the procedure to their respective potential complications, thereby maximizing benefits. Limb preservation, wound healing, and amelioration of pain should be the primary goals. Some patients with CLI may be best treated with palliative measures.

4. Risk Factors and Management

Identification and modification of risk factors may stabilize and in some cases cause regression of atherosclerotic plaque throughout the vascular beds in the body thereby lessening the risk of MI, stroke, or limb ischemia. This section will review the risk factors associated with the development of PAD and their respective treatment strategies.

4.1. Smoking

Smoking is an independent risk factor for the development of PAD. It has also found to be associated with an increased risk of PAD progression, subsequent risk of amputation, MI, and death. There is a seven fold increased risk in developing PAD in ex-smokers compared to patients who never smoked. This risk increases to 16 fold in patients who actively smoke. (Cole et al, 1993) The severity of PAD has been shown to be directly proportional to the quantity of smoking. Smoking cessation is imperative in patients with PAD. Cessation is associated with increased walking distances in claudicants, lower risk of amputation, and decreased likelihood of bypass thrombosis in those patients who have undergone revascularization and improved survival. Addiction remains a major impediment, with many patients experiencing recidivism. Smoking

cessation programs, nicotine replacement, and antidepressants may assist in patients in quitting.

4.2. Diabetes

Diabetes is associated with over a twofold increase risk in developing PAD. (Norgren et al, 2007) The incidence of diabetes in both industrial and developing nations has been climbing. Patients with both PAD and diabetes are at greater risk of lower extremity amputation compared to those patients with PAD alone due to associated neuropathy and impaired immunity. Diabetics are also at increased risk for major amputation due to higher incidences of acute arterial thrombosis.

Anatomically, atherosclerotic lesions in the lower extremities of diabetics tend to be more frequently diffusely distributed and located distally, particularly in the tibioperoneal trunk and tibial vessels. Proximally, the aorta, iliac and femoral arteries are commonly spared. Diabetics are also at elevated risk of MI, stroke and death. Given these associations current guidelines call for hemoglobin A1c target values of less than 7%. (Percentage Tight glycemic control only is proven to be beneficial in preventing microvascular complications (neuropathy, retinopathy, nephropathy). (American Diabetes Association, 2012)

4.3. Dyslipidemia

Studies have shown a relationship between the reduction of Low Density Lipoproteins (LDL) and the development of major vascular events, including the incidence of coronary heart disease. (Beignet et al, 2005) Risk modification in patients with PAD should include dietary changes and the addition of statins to achieve LDL levels less than 100mg/dL and lower than 70mg/dL in patients with multiple risk factors. (NCEP, 2002) Levels of High Density Lipoprotein (HDL) below 40mg/DL have been associated with increasing incidence of cardiovascular disease. HDL may be elevated by exercise, smoking cessation, dietary modification, weight loss, and the addition of niacin and/or fibrates.

4.4. Hypertension

Although the association between hypertension and PAD are not strong, the main benefits of antihypertensive therapy come with the reduction of complications associated with cerebro-vascular and coronary artery disease. Lifestyle modifications should include exercise, weight loss, and limitations on sodium intake. Antihypertensives should be administered to achieve a goal blood pressure of less than 140/90mmHg and lower in patients with co-morbidities such as diabetes and renal insufficiency. (Norgren et al, 2007)

4.5. Exercise

In patients with claudication, exercise has been shown to improve walking ability and increase walking distances, with improvements in distances of up to 180%. (Gardner and Poehlman, 1995) However, optimal results require structured exercise regimens

with current recommendations calling for 30 minutes of training, three times per week. When combined with dietary modification exercise may also decrease the incidence of diabetes resulting in lower secondary mortality from cardiovascular events.

4.6. Chronic Renal Insufficiency

Patients with chronic renal insufficiency have an overall risk of PAD, which is three times greater when co-morbid conditions such as diabetes, CAD, and stroke are matched. (O'Hare and Glidden, 2004) Studies have demonstrated a direct association between the likelihood of presenting with severe critical limb ischemia as opposed to rest pain with worsening renal function. A similar association is seen with one year mortality risk. (O'Hare et al, 2005) Preservation of renal function may decrease the risk of PAD progression.

5. Pharmacotherapy

The most common pharmacotherapy used to treat PAD is antiplatelet agents, anticoagulants, and phosphodiesterase inhibitors. Among antiplatelet agents who inhibit platelet aggregation, aspirin, and thienopyridines are most commonly administered. Aspirin irreversibly inhibits platelet cyclooxygenase-1. It has been shown to reduce PAD, cardiovascular and neurovascular events. Low dose aspirin maintains these protective effects with minimal risk of gastrointestinal bleeding.

Thienopyridines also irreversibly inhibit platelet aggregation, by binding to Adenosine Diphosphate ADP receptors. Clopidogrel is the most commonly administered thienopyridine. The CAPRIE trial demonstrated a 24% relative risk reduction in myocardial infarction, stroke, and vascular death when Clopidogrel (Trade name: Plavix) was compared to Aspirin in patients with PAD. (CAPRIE Steering Committee, 1996) Combining ASA and Plavix has not been shown to be of any additional PAD related and antiplatelet agent for all symptomatic patients with and without a history of cardiovascular disease. (Norgren et al, 2007)

The mainstay of anticoagulants is oral warfarin. It a Vitamin K antagonist, inhibiting the hepatic synthesis of Vitamin K dependent factors II, VII, IX, X protein C and S. Warfarin therapy must be monitored and this is typically performed with an International Normalized Ratio (INR) with a goal for therapy of 2.0 to 3.0. Complications may include hemorrhage and skin necrosis. Pregnancy is a contraindication to use. Warfarin may be beneficial either alone or in combination with aspirin in patients who have undergone infra-inguinal bypass, and are at high risk of bypass thrombosis and limb loss. (Clagett et al, 2004)

Cilostazol is a phosphor-diesterase inhibitor and functions by causing vasodilation and inhibiting platelet aggregation. It is used for the relief of claudication symptoms and has been demonstrated to increase walking distances. Congestive heart failure is a contraindication to its use.

6. History and Physical

6.1. Claudication

The patient with chronic ischemia of the lower extremity may present with claudication, rest pain, or tissue loss, with the majority of patients complaining of intermittent claudication. The etymology of claudication derived from Latin and means 'to limp'. The primary complaint is pain, described as fatigue, cramping or aching involving the calf, thigh or buttocks, which is brought on with ambulation and relieved with rest. Pain described as shooting or not relieved by rest is unlikely to be related to arterial insufficiency and other etiologies must be ruled out, including musculoskeletal, neurogenic, rheumatologic, or venous. The patient's co-morbidities should also be assessed, as they may be the rate limiting steps in the patient's ability to ambulate; this may include cardiac or musculoskeletal disease. Optimizing cardiac hemodynamics may resolve or improve claudication symptoms. The patient should be asked about the number of blocks they can ambulate until they must stop due to pain. This value should be monitored on follow-up for improvement with risk factor modification and exercise regimens.

The physical exam should include a comprehensive evaluation of the vascular system. Findings should encompass cardiac rate and rhythm, extremity pulses (including bilateral femoral, popliteal, dorsalis pedis and posterior tibial pulses), auscultation of the carotids arteries for bruits, and palpation of the abdomen, groins and popliteal fossa for aneurysms. The lower extremities should be examined for muscle atrophy, skin color and temperature, capillary refill, toenail quality, and hair growth or loss.

The location of symptoms and the presence or absence of associated pulses may help determine the anatomic distribution of atherosclerotic involvement. Typically ischemic symptoms involve the muscle groups just distal to the level of arterial stenosis or occlusion. Patients with multisegmental vessel involvement may have symptoms of claudication involving multiple muscle groups. However, most claudicants will have a single segment of vessel stenosis or occlusion with distal perfusion being supplanted by collateral vessels. By comparison, patients with CLI will typically have multilevel arterial occlusions, placing the limb at greater risk. Claudication of the buttocks and thighs corresponds to involvement of the aorta or iliac arteries, while claudication of the calves reflects femoro-popliteal artery involvement. Some patients with iliac artery stenosis or occlusions may have Leriche syndrome, which is the triad of intermittent claudication, vasculogenic impotence and absent or diminished femoral pulses.

Pulses are graded on a scale of 1-5. If the quality of the pulse is normal, it is rated as 3+, weak pulse-2+, and very weak pulse-1+. If not palpable 0, and aneurysmal pulse is rated as 4+. When one feels thrill over the area of pulse, we usually put a square mark on the pulse noted. If pedal pulses are palpable, the patient is unlikely to have clinically significant PAD, and other differentials must be evaluated to explain the patient's symptoms.

In addition to the physical exam, non-invasive tests are essential to confirm the diagnosis and determine the anatomical distribution of disease involvement. Patients

without palpable pulses should undergo a non-invasive study, preferably an ankle brachial index (ABI) and pulse volume recording (PVR).

As mentioned above, a major significance in establishing a diagnosis of PAD, is the recognition of elevated cardiovascular and neurovascular complications. The patient with a confirmed diagnosis of PAD, even without associated symptoms, can then be marked for an intensified regimen of risk factor modification.

6.2. Critical Limb Ischemia

Symptoms in patients with CLI include rest pain and tissue loss. Rest pain is typically described as burning along the distal most aspect of the extremities, including the toes, metatarsals and any existing ulcers. Symptoms should be present for two weeks or more. Pain may be alleviated by placing the lower extremity in a position of dependency. Ulcers, if present, may be primarily ischemic in origin, or secondary to venous hypertension or neuropathy, trauma or infection with failure to heal due to the underlying arterial insufficiency. Arterial ischemic ulcers are usually located on the toes, foot, or ankle.

Physical exam should include components noted in the prior section. Additional classical findings, which correlate with CLI, include dependent rubor, and pallor with elevation. These findings are indicative of severe arterial insufficiency, where the action of gravity alters perfusion. Dependent rubor is redness of the foot when the limb is lowered, which is reversed to pallor when it is elevated. A foot that is dusky, cool and with delayed or absent capillary refill is likely acutely threatened.

Non-invasive studies in patients with CLI typically have ABI values below 0.40, and toe pressures below 30mmHg.

Patients presenting with CLI by definition have inadequate blood flow to the extremity at rest and are at high risk of limb loss without revascularization, via either endovascular or surgical means. This process is in direct contradistinction to patients presenting with claudication who are at low risk of limb loss, and who do not require revascularization.

7. Diagnostics

7.1. Non-Invasive Studies

Non-invasive studies form the basis of diagnostic evaluation of patients with chronic ischemia of the lower extremities and include the Ankle Brachial Index (ABI) and Pulse Volume Recording (PVR). The ankle-brachial index is determined by using a sphygmomanometer in conjunction with a Doppler probe to measure the systolic pressures of the dorsalis pedis and posterior tibial arteries, which are then divided by the systolic pressure of the brachial artery. An ABI lower than 0.9 is indicative of PAD, and the presence of hemodynamically significant occlusive disease between the heart and ankle. It is also indicative of an increased risk of future cardiovascular events, with such patients having a three to six fold increased risk of cardiovascular mortality. Some

patients with claudication may have a normal ABI. This may be because the pressure decrease over a stenosis only becomes clinically significant with the increased demand associated with ambulation. These patients may require the ABI be measured after a period of exertion, such as a standardized walk on a treadmill, or a series of heel raising exercises. The ABI may be falsely elevated in patients with diabetes and chronic renal insufficiency due to calcification of the vessels, resulting in falsely elevated systolic pressures. These patients require further evaluation, with either PVRs, or toe systolic pressures. An ABI lower than 0.4 correlates with diagnosis of CLI.

Once the diagnosis of PAD has been confirmed with non-invasive studies, it needs to be determined whether the symptoms warrant intervention or an intervention. Most patients with claudication should undergo risk factor modification, exercise regimens, and pharmacotherapy discussed earlier. Exceptions to this may include patients who have claudication, which severely affects their quality of life and activities of daily living. These patients should be evaluated for possible revascularization, in particular if the lesion is localized proximally.

7.2. Imaging: Duplex Ultrasound, CTA, MRA, and Angiography

Prior to revascularization, anatomical studies are required to define the location and morphology of the involved lesion/lesions. Results of these studies help determine the feasibility of various invasive open and endovascular options.

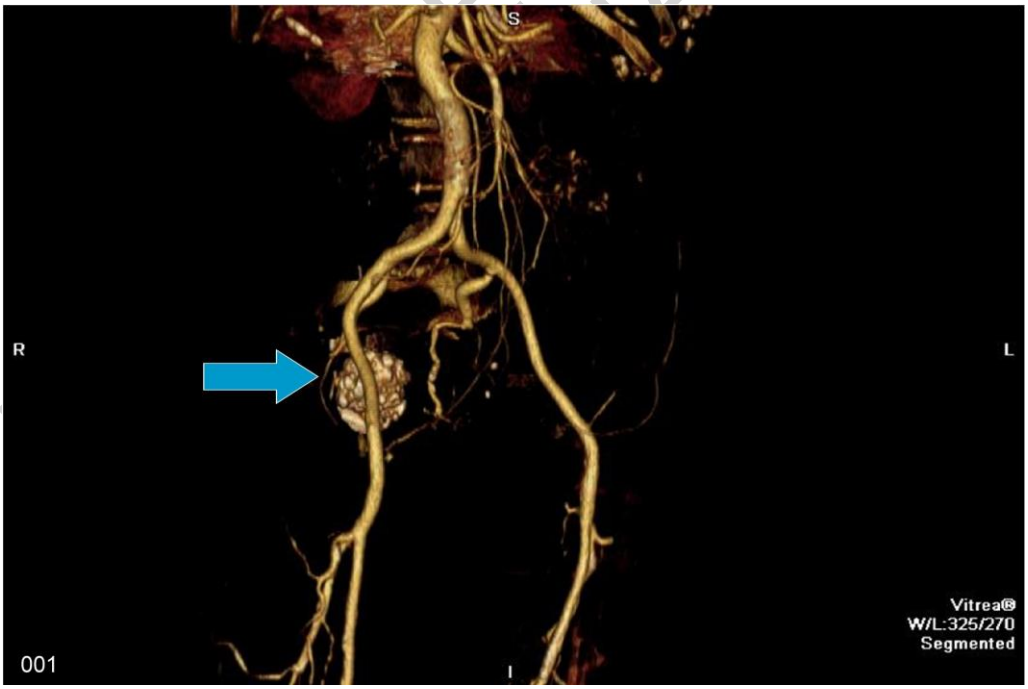

Figure 1. CTA film of aorto-iliac arteries and proximal femoral arteries. Arrow—non-vascular mass with calcification.

Duplex ultrasonography is a non-invasive, inexpensive test. It is used to localize and characterize lesions by direct visualization, and by measuring velocities of blood flow. This modality can be time consuming and is highly operator dependent.

CTA and MRA are the standard non-invasive imaging studies perform at many centers. These studies are expedient, and provide accurate reconstructions of patient's abdominal, pelvic, and lower extremity vasculature. Both CTA and MRA are excellent modalities in assessing patient's inflow and outflow vessels. In patients with heavily calcified vessels, MRA is preferable as it is less subject to artifact.

Figure 2. CTA film of bilateral ilio-femoral arterial system.

Both modalities require the administration of intravenous contrast. Contrast used in CTA studies is iodinated, which may result in an allergic or nephrotoxic reaction. Current MRA studies are performed with intravenous gadolinium, which puts patients with renal insufficiency at risk for nephrogenic systemic fibrosis. CTA expose the patient to more radiation, than a single chest X-ray, so this test must be carefully considered.

Certain foreign implants may not be MRI compatible, and thus, be a contraindication to MRA while other devices which are MRI compatible, may result in severe artifact, making the study non-diagnostic. Although CTA will also result in streak artifact in patients with foreign bodies, they will be less prominent and thus CTA is the study of choice in these patients. CTA is performed faster than MRA, thus may be ideal in patients who have a limited tolerance of enclosed spaces or ability to remain still.

Although angiography remains the gold standard in the imaging of the lower extremity vascular system, given its invasive nature, it is not typically used pure diagnostic purposes. Angiography requires arterial puncture, contrast administration, exposure to radiation, is time intensive, and may be operator dependent. Angiography is usually reserved for planned endovascular interventions, or to further delineate suitable inflow and outflow vessels for bypass.

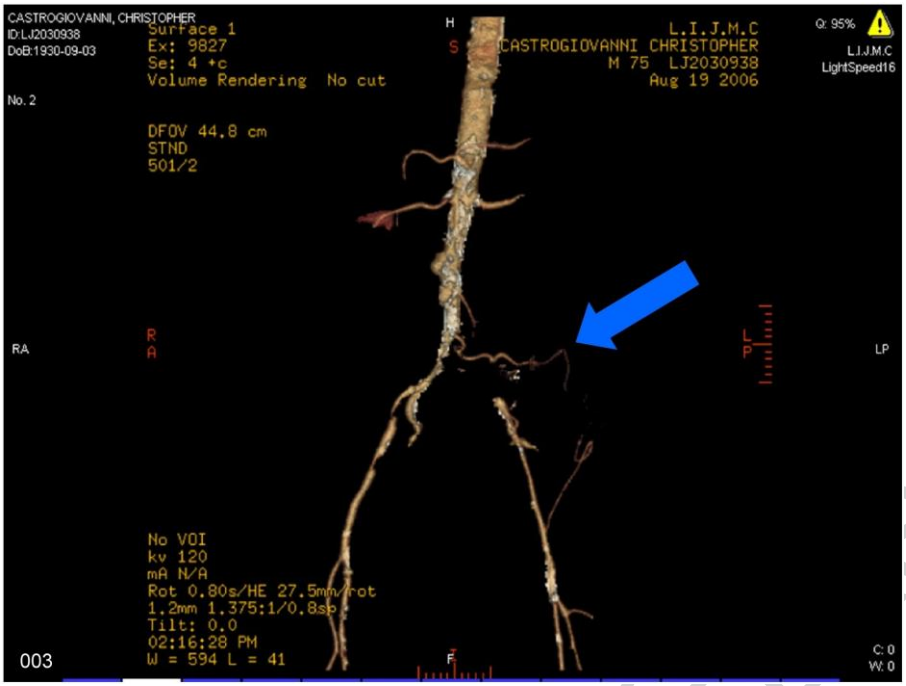

Figure 3. CTA film showing occlusion of left common iliac artery (arrow) with disease at the contralateral iliac artery.

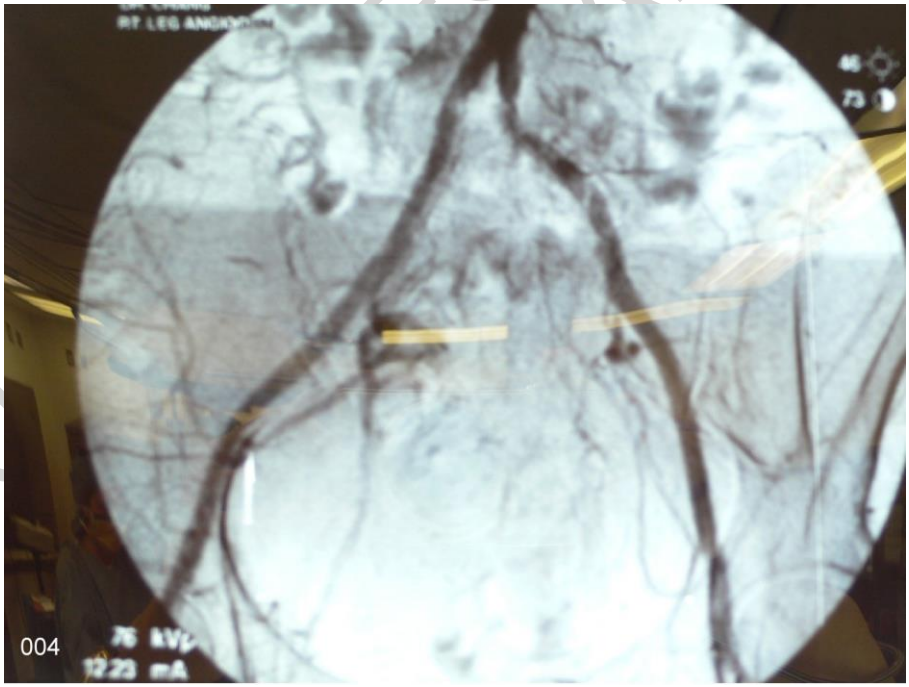

Figure 4. Angiogram showing distal aorta and bilateral iliac arterial system.

Prior to proceeding to interventions, it is essential to determine the anatomic location and quality of lesions involved. Both the inflow and outflow vessels must be evaluated, as both play an important role in patency of intervention.

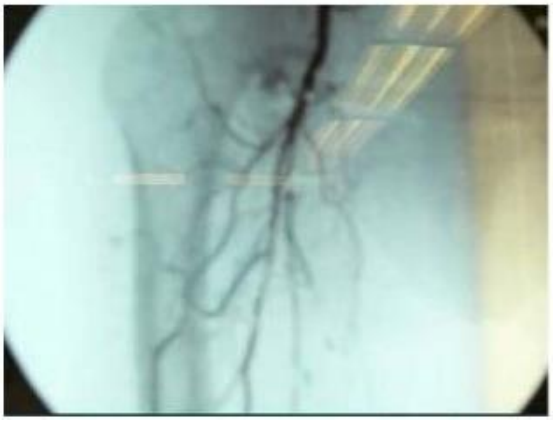

Figure 5 and 6. Angiograms showing right ilio-femoral arterial system and right femoral arterial system.

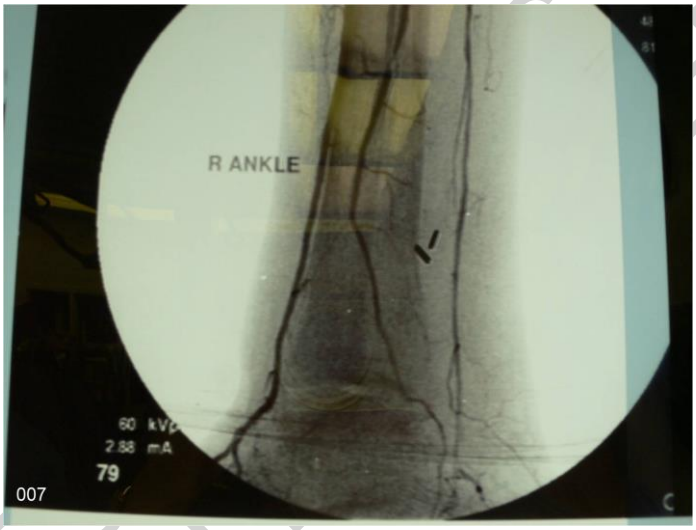

Figure 7. Angiogram showing right ankle area.

Figure 8. Angiogram showing right foot area.

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Biographical Sketches

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Robert W. Chang is a board certified vascular and endovascular surgeon. He is a member of the Society for Vascular Surgery, a fellow of the American College of Surgeons as well as the San Francisco and Yale Surgical Societies. He completed his surgical residency at Yale-New Haven Hospital in New Haven, Connecticut, and his vascular fellowship at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire. He has authored numerous book chapters, peer-reviewed articles and has presented his work many times throughout his surgical career. He lives in San Francisco, California, and practices vascular and endovascular surgery in a large multispecialty group.

John B. Chang is a board certified vascular surgeon with many years of experience. His academic appointments include Professor, Clinical Surgery, Hofstra Northshore-LIJ School of Medicine, Uniondale, New York; Adjunct Professor, Clinical Surgery, Albert Einstein School of Medicine, Bronx, New York, and MD Appointment Committee, Department of Surgery, Hofstra Northshore-LIJ School of Medicine, Uniondale, New York. He is currently, Director, Long Island Vascular Center, Roslyn, New York, and Senior Attending Surgeon, Northshore-LIJ Healthcare System, New Hyde Park, New York. He is Chairman, Board of Directors, International College of Angiology, Editor-in-Chief, *International Journal of Angiology*, and Founding Chairman of the Asian Society for Vascular Surgery. He has authored numerous books, and published many articles regarding the medical and vascular surgical management of patients. He has received numerous citations and awards for his work in vascular surgery.