In the decade ahead, patients and primary care physicians will increasingly recognize the clinical burden of peripheral arterial disease (PAD). As new advances in the treatment of coronary artery disease continue to reduce mortality and morbidity, caregivers will increasingly confront the problem of concomitant “noncoronary” arterial disease. Cardiovascular physicians should assume a more proactive clinical role, along with their vascular medicine colleagues, to encourage new therapeutic opportunities for the treatment of arterial disease affecting multiple vascular beds. Multivascular therapeutic approaches are needed because atherosclerosis has a common systemic pathogenesis and simultaneously affects multiple circulations.

Deployment of PAD therapies must be guided by an appreciation of the diverse natural histories associated with peripheral arterial diseases. Ideal patient-focused clinical outcomes may be defined when: (1) coronary therapies improve myocardial perfusion, reduce the risk of myocardial infarction and heart failure, and improve patient survival; (2) carotid therapies permit survival with reduced incidence of stroke; (3) renal artery disease therapies diminish the need for renal replacement therapies (dialysis and transplantation); and (4) lower-extremity PAD therapies improve functional status, foster wound healing, and decrease amputation rates. The achievement of health without amputation, stroke, end-stage renal failure, or myocardial infarction will require clinical wisdom. The calculation of risk/benefit ratios becomes increasingly complex with multicirculation intervention and should be calibrated to the individual at risk.

Patients with diffuse atherosclerotic disease traditionally have sought consultation and care from multiple specialists. The subspecialty of vascular medicine provides coordinated diagnostic and therapeutic efforts using a team approach. The case examples discussed below illustrate the integrated management of patients with vascular disease in the coronary, subclavian, carotid, renal, and lower-extremity circulations.

Case 1
A 76-year-old man with a history of hypertension, hypercholesterolemia, and tobacco use presented to the hospital with sudden severe pulmonary edema and was referred for cardiac catheterization. Five months earlier, an aortogram performed at another hospital to assess peripheral arterial disease showed “mild stenoses affecting the origins of the renal arteries.” During the current admission, he required intubation because of the severity of pulmonary edema associated with a blood pressure of 230/110 mm Hg and related transient ST depression in the anterior leads. He initially improved with administration of intravenous nitroglycerin, furosemide, and fenoldopam, with rapidly improving oxygenation, and resolution of the ischemic electrocardiographic changes. Nevertheless, within the first day of hospitalization, his troponin-I level increased to 0.6 ng/mL (normal range is less than 0.5 ng/mL) and his serum creatinine level rose from 1.2 to 2.3 mg/dL. Sudden pulmonary edema in association with azotemia and evidence of an acute coronary syndrome (ACS) suggested the possibility of renal arterial disease as a contributor to his cardiac deterioration. The risks and benefits of immediate evaluation of...
both coronary and renal arterial systems were discussed with the patient versus deferring this to a future date, based on the unpredictable risk of recurrent episodes of ACS and pulmonary edema provoked by renal arterial disease. After treatment with nasogastric acetylcysteine, he underwent coronary angiography that showed diffuse 3-vessel coronary artery disease, an ejection fraction of 50%, and a left ventricular end-diastolic pressure of 28 mm Hg. Aortography demonstrated bilateral severe renal artery stenoses that were treated with angioplasty and stent placement (Figure 1). His blood pressure improved and his serum creatinine decreased to 1.3 mg/dL in the subsequent 2 days. At that time, he underwent coronary artery bypass grafting and was discharged after an uneventful recovery.

Discussion
Although cardiovascular clinicians often are presented with the opportunity to perform immediate invasive evaluation for acute coronary syndromes, characterized by ischemic symptoms and signs in association with small elevations in serum troponin values, the pathophysiology of this patient’s clinical presentation offered clues that his pulmonary edema may have had both nephrogenic and cardiogenic etiologies.

Renovascular disease, when severe, may cause volume-dependent or renin-dependent hypertension, ischemic nephropathy, or sudden pulmonary edema; however, bilateral renal artery disease is more closely associated with development of “flash” pulmonary edema than is unilateral renal artery disease. Bilateral renal artery disease markedly limits the ability of the available nephron mass to compensate for the increased sodium retention with a natriuresis. In chronic bilateral renal artery disease, long-term volume expansion inhibits renin secretion and this minimizes vasoconstriction induced by angiotensin II. However, with the imposition of acute coronary ischemia, it is presumed that renal sympathetic activity, additional renin-angiotensin system stimulation, and volume-dependent hypertension and intravascular volume expansion all predispose the patient to homeostatic decompensation, with consequent pulmonary edema.

Atherosclerotic renal artery stenoses (RAS) are commonly encountered in certain cohorts of patients who undergo cardiac catheterization, such as those who present with an elevated serum creatinine, a history of peripheral arterial or carotid artery disease, or a high atherosclerotic risk factor burden.1 Atherosclerotic disease producing greater than a 50% stenosis in at least 1 renal artery is found in 30% of patients who present to the catheterization laboratory with coronary artery disease, 38% of patients with abdominal aortic aneurysm, and 39% of patients with iliofemoral disease.2 Approximately 1 in 3 patients with RAS has bilateral involvement.

The progression of RAS is generally a slow process. A serial observational study has suggested that the incidence of renal artery atherosclerosis progression from a 60% stenosis to total occlusion is approximately 10% after 3 years.3 For the patient in this discussion, as for most individuals who present in a comparable way, data are lacking that can define whether RAS progression served as the primary stimulus for cardiovascular decompensation or if a systemic factor (dietary sodium load, medical noncompliance, or plaque rupture) served as the “renal physiological trigger.”

A more complete description of the pathophysiology of renal artery stenosis has been reviewed elsewhere.4 Our knowledge base regarding the natural history and relative risk and benefit of percutaneous intervention has been slowly augmented, but remains incomplete. The scientific evidence is composed primarily of case series of patients undergoing renal artery stenting and has defined clinically significant renal arterial disease as stenoses greater than 50%. Only a single report has attempted to define the “clinical significance” of a renal artery stenosis.
in an experimental setting. Imanishi and colleagues\(^3\) observed that greater than 75% diameter stenosis was required to cause a detectable rise in blood pressure in dogs.

The optimal treatment for RAS continues to evolve, and yet recent experience suggests that use of balloon angioplasty alone is not optimal. Three randomized studies have compared balloon angioplasty alone with medical therapy in a total of 210 hypertensive patients with greater than 50% diameter stenoses of at least 1 renal artery and with diastolic blood pressures greater than 95 mm Hg. In these reports, there were no significant differences or trends in serum creatinine values between the treatment groups during 3 to 54 months of follow-up.\(^6\)–\(^8\)

Renal artery stenting is probably superior to balloon angioplasty for the treatment of RAS. The rates of restenosis after renal artery stenting at 1 year range from 11% to 19%\(^9\)–\(^11\) but the relevant long-term clinical benefits can be variable and difficult to predict for each treated individual. This may not be surprising as the mechanisms underlying hypertension are complex and incompletely understood; renal artery perfusion is but one contributor to long-term blood pressure control. From an optimistic perspective, as many as 40% to 60% of individuals enjoy an improvement in blood pressure control after successful renal percutaneous transluminal angioplasty (usually defined by a need for fewer antihypertensive medications). Several investigations have, however, also described the limitations of renal stenting in that only 4% to 18% of patients undergoing renal artery stenting experience “cured” hypertension. As well, as many as 22% to 61% of the treated patients show no improvement in blood pressure control at all.\(^9\)–\(^12\) The treatment of bilateral renal artery disease is more likely to improve blood pressure control than the treatment of unilateral disease.\(^9\) It is therefore important for patients, who have experienced frustration with use of multiple medication combinations to achieve target blood pressure levels, to be appropriately informed of variable outcomes from renal stenting. Clinical benefit of renal stenting is most likely when a significant proportion of the functioning nephron mass is jeopardized by severe renal artery stenoses. In other words, stenting severe bilateral renal artery stenoses (greater than 75%) or a severe stenosis affecting a single functioning kidney is more likely to provide clinical benefit than stenting an incidental unilateral 50% stenosis.

Serum creatinine levels generally remain unchanged after renal stenting. Although renal stenting and percutaneous transluminal angioplasty may be applied to improve blood pressure or theoretically to preserve renal function (to delay progression of RAS to end-stage renal disease), the immediate effect on serum creatinine levels in large series is inconsistent. Worsening renal function after the procedure (manifested by rising creatinine levels) may be caused by atheroemboli. Renal atheroembolization may be reduced by the use of the no-touch technique to minimize aortic wall trauma with guide catheters.\(^13\) This is an important issue because creatinine levels are a strong predictor of long-term survival after renal interventions. In one study, the 3-year mortality was 40% when the baseline creatinine level was greater than 2 mg/dL but was only 5% when it was less than 1.5 mg/dL.\(^14\)

Routine renal angiography during cardiac catheterization is neither currently encouraged nor reimbursed. The currently available (temporary) “G” code for renal angiography during concomitant coronary angiography is associated with reimbursements of approximately US $10. The future role of renal angiography during coronary angiography will be addressed in the 2004 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Peripheral Arterial Disease. The indication for renal angiography during concomitant coronary angiography is generally deemed acceptable when there is clear prospective documentation of clinically significant RAS, as suggested by such critical conditions as flash pulmonary edema or malignant hypertension complicated by an acute coronary syndrome, with a preprocedural signed consent. For selective patients in clinical practice, renal angiography and renal stenting can be beneficial as techniques improve, the clinical-trial database becomes more robust, and clinical-care guidelines are diligently applied.

**Case 2**

A 69-year-old man was referred for cardiac catheterization because of a 2-month history of worrisome atypical progressive chest pain that had markedly impeded his lifestyle. These rest and exertional chest pain symptoms were only minimally improved by an empiric antianginal therapeutic program and were not altered by use of H2-antagonists or proton pump inhibitors. His past medical history was significant for hypertension and diabetes mellitus, but he had no history of cerebrovascular disease (ie, no stroke or transient ischemic attack). Physical examination showed an overweight man in no distress with mildly elevated blood pressure of 142/85 mm Hg, a right carotid bruit, an S4 gallop, and normal peripheral pulses. A nuclear stress test showed reversible inferior and anterior myocardial perfusion defects. Cardiac catheterization showed an ejection fraction of 40% and severe 3-vessel coronary artery disease with focal stenoses in the proximal left anterior descending artery, first marginal branch, and mid-portion of the right coronary artery, along with adequate distal target segments for bypass surgery. Carotid angiography showed a 90% stenosis at the origin of the right internal carotid artery (Figure 2). He underwent prophylactic carotid endarterectomy (CEA) before bypass surgery.

**Discussion**

High-grade carotid stenoses of greater than 80% occur in 8% to 12% of
patients scheduled for coronary artery bypass grafting (CABG), even in asymptomatic patients, and are responsible for up to 30% of hemispheric strokes that occur early after surgery. Perioperative stroke risk is less than 2% when carotid stenoses are less than 50%, but the risk rises to approximately 10% when stenoses are 50% to 80% and increases to 11% to 19% when stenoses are greater than 80%. Patients with bilateral high-grade stenoses or occlusions have up to a 25% chance of stroke.

Current guidelines recommend carotid endarterectomy for patients with severe extracranial carotid vascular disease before or at the same time as CABG, because it is associated with a lower risk of significant neurological complications than carrying out CABG in the presence of high-grade carotid stenoses. Despite published guidelines, extensive controversy about the recommendations still persists. On the one hand, it has been reported that carotid endarterectomy performed in this fashion carries a relatively low mortality (3.5%), reduces early postoperative stroke risk to less than 4%, and is associated with a 5-year freedom from stroke of 88% to 96%. On the other hand, stroke risk may be increased if a "reversed-stage" procedure is used, in which the coronary bypass operation precedes the carotid endarterectomy by more than 1 day. Equally importantly, the risk of myocardial infarction may be increased if CEA precedes CABG.

Decisions about the use of staged, synchronous, or single-vascular bed surgery must be individualized and based on the severity of presenting symptoms, extent of vascular disease affecting either circulation, and concomitant nonvascular co-morbidities. It is reasonable to follow the sequence of CEA followed by CABG, as illustrated in this case, when the risk of cardiac decompensation on β-blocker therapy during CEA is minimal. For patients with critical left main coronary artery disease, however, or refractory unstable angina and multivessel coronary artery disease requiring urgent CABG, a synchronous or reverse-stage procedure of CABG followed by CEA may be more appropriate.

Another area of controversy involves the anatomic diagnosis of carotid disease. The exact role of various noninvasive versus angiographic methods undoubtedly depends on the accuracy of duplex and magnetic resonance angiography techniques and the experience and outcomes at each institution. One study has recommended a return to conventional cerebral angiography for surgical decision-making, because duplex ultrasound alone produced a high false-positive rate of approximately 40%. The combined approach of Doppler ultrasound and magnetic resonance angiography together may be more accurate than either method alone. Noninvasive methods may be most helpful when they offer reliable data in ruling out high-grade disease and averting the need for additional angiographic risk. For example, individuals less than 65 years old or those with fewer atherosclerotic risk factors or less severe coronary disease are less likely to have high-grade asymptomatic carotid artery disease. In contrast, in individuals at high risk of severe carotid disease, a direct approach to cerebral angiography may offer several advantages. Contrast angiography offers a precise determination of the severity of carotid stenoses and identifies conditions that may be unfavorable for carotid endarterectomy, such as intracranial disease or carotid occlusions. Contrast angiography can also identify anatomic features that make endovascular treatment difficult, such as a markedly distorted aortic arch, carotid artery tortuosity, thrombus, occlusion, or heavy calcification. When an assessment of pre-CABG carotid anatomy is indicated, and when a coronary angiographic procedure is required, imaging of both arterial circulations can be considered at the same sitting. The cardiac cathe-
terization laboratory with a large image intensifier of 12 inches or greater provides adequate imaging to perform carotid angiography. Cineangiography is superior to cut film to show mobile thrombus, which is a contraindication to stenting without distal vascular protection.

Carotid stenting requires proof of its safety and efficacy relative to that of CEA. Several studies have reported success with carotid stenting. The CaRotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) randomized 304 patients with carotid stenosis to endovascular treatment or CEA. The rates of disabling stroke or death within 30 days of treatment did not differ significantly between the 2 groups (6.4% versus 5.9%, respectively). One limitation of the study was that stents were used in only 26% of the patients randomized to carotid intervention and that the 5.9% rate of disabling stroke or death within 30 days of CEA was higher than anticipated.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial is a randomized trial of carotid stenting with distal protection versus CEA in patients with significant comorbidities. Results presented at the AHA Scientific Sessions in 2002 showed superior results for stenting (Precise, Johnson & Johnson) with distal protection (AngioGuard, Johnson & Johnson) in high-risk patients. Eligible patients were asymptomatic with greater than 80% stenosis by ultrasound or symptomatic with greater than 50% stenosis and at least 1 high-risk feature such as age greater than 80 years, congestive heart failure, severe chronic obstructive pulmonary disease, previous CEA with restenosis, previous radiation or radical neck surgery, or high lesions difficult to access. After multispecialty screening by a vascular surgeon, interventionalist, and a neurologist, patients were randomized. The trial was stopped early because of slowing enrollment after a total of 307 patients were randomized to stenting plus distal protection (n=156) or CEA (n=151).

It is not clear how stenting with distal protection compares with CEA in younger patients at lower risk during CEA. To answer this question, the National Institutes of Health sponsored the Carotid Endarterectomy Stent Trial (CREST) to compare CEA with carotid stenting in 2500 patients with internal carotid stenoses greater than 50% (by angiography) or 70% (by ultrasound). The primary end points of the study will be the 30-day composite incidence of stroke or death and 4-year incidence of ipsilateral stroke. The problem of slow initial enrollment was ostensibly solved in 2003 after collaboration with the Centers for Medicare and Medicaid Services, allowing reimbursement for carotid stenting in the setting of the randomized trial.

Carotid stenting is a reasonable approach for patients who need CEA but who are considered high-risk candidates for surgery because of severe coexisting medical illness, prior surgery, or prior neck scarring. The most promising advance for carotid stenting is the use of distal vascular protection (Figure 3).27 As noted above, several unpublished registries and experiences have been reported and some concern exists about embolization caused by catheter manipulation required for placement of distal protection devices. Additional guidelines and limited approval for carotid stenting with distal protection are anticipated in 2004.

Case 3
An 84-year-old woman was referred for cardiac catheterization for intractable angina. The patient had a history of new exertional angina 3 months before admission, and she underwent coronary artery bypass surgery at that time, with a left internal mammary graft to the left anterior descending artery and saphenous vein grafts to the first obtuse marginal branch and posterior descending artery. Although she recovered uneventfully, severe angina persisted. Repeat cardiac catheterization showed 3 patent grafts, but the left internal mammary graft was jeopardized by severe stenoses affecting the left subclavian artery (Figure 4). After stenting of the subclavian artery, the angina resolved.

Discussion
Preoperative assessment of patients before coronary artery bypass surgery includes the comparison of blood pressure measurements in both arms to exclude significant subclavian disease that may interfere with success of the left internal mammary graft. Selective left subcla-
vian angiography is indicated at the time of cardiac catheterization for patients with suspected subclavian disease who need coronary artery bypass surgery. It should be emphasized, however, that pseudolesions caused by respirophasic kinking of the subclavian arteries should be assessed by appropriate maneuvers (Figure 5).

Risk factors for atherosclerotic disease of the upper extremity are identical to those for atherosclerosis in coronary or lower-extremity arteries; other etiologies specific to the upper extremity include Takayasu’s arteritis, radiation-induced atherosclerosis, trauma, and thoracic outlet syndrome. The incidence of severe obstruction in the subclavian and brachiocephalic (innominate) arteries is lower than that in the iliofemoral systems, and symptoms are also less frequent because of both the lower metabolic work required for most individuals (few reach the threshold for arm claudication) and the propensity for formation of collaterals around the shoulder and scapula.29

Most subclavian atherosclerotic stenoses exist in the absence of symptoms and a documented adverse natural history. Most are found incidentally when bilateral arm blood pressures are found to be discordant and require no local treatment. Their presence does mark a patient in whom atherosclerosis risk-factor goals should likely be intensified to those of a patient with any other form of atherosclerotic disease, such as coronary or carotid artery disease. Percutaneous treatment of atherosclerotic obstruction of the subclavian or brachiocephalic vessels should be considered for patients who experience reproducible arm claudication, subclavian steal syndrome, distal hand atheroembolism,30 or impaired inflow into internal mammary grafts, axillofemoral bypasses, or dialysis access fistulas.

Experience with subclavian or brachiocephalic stenting is limited to case reports and small series, but it appears that stenting may be superior to balloon dilatation alone.31 A small series of 18 consecutive patients was treated with 100% success and no complications.32

Case 4
A 41-year-old man was referred for cardiac catheterization and angiography because of right leg claudication and a positive stress test for myocardial ischemia. The patient smoked 2 packs of cigarettes a day for 29 years and planned to quit. He had one-block right-thigh claudication that interfered with his job as construction worker. Physical examination was normal except for absence of right femoral, popliteal, and pedal pulses. A noninvasive myocardial perfusion study showed a moderate reversible inferior myocardial defect. He underwent a segmental pressure examination in the vascular laboratory and had a normal left leg arterial assessment, but an abnormal right leg ankle-brachial index value of 0.72, with pressure gradients and Doppler waveform abnormali-
amputation is unusual in patients with the major common risk factors. and hypercholesterolemia also serve as of premature atherosclerotic disease, whereas hypertension, family history relative risk for PAD than CAD, those for coronary artery disease. Diabetic peripheral arterial disease are similar to vascular repair. The risk factors for pe-

Discussion

The anatomic pattern of atheroscle-
rotic obstructive disease in the distal aorta and iliofemoral arteries varies with age. In patients less than 40 years of age, aortoiliac disease is the most common site of atherosclerosis. In patients older than 40 years, femoropopliteal disease accounts for more than 65% of anatomic sites that lead to claudication symptoms. Approximately two-thirds of patients with iliac disease will have stenoses, whereas two-thirds of patients with femoral disease have occlusions, and most of these are characterized by long segmental occlusions. Thus, successful long-term percutaneous revascularization of the femoral arterial segment is more challenging than iliac endovascular repair. The risk factors for peripheral arterial disease are similar to those for coronary artery disease. Diabetes and smoking connote a higher relative risk for PAD than CAD, whereas hypertension, family history of premature atherosclerotic disease, and hypercholesterolemia also serve as the major common risk factors.

Progression to severe ischemia or amputation is unusual in patients with intermittent claudication, occurring in only approximately 1.4% of patients per year. The progression of disease and its complications is markedly amplified in individuals with either a history of diabetes or current smoking. In the absence of these risk factors, the risk of limb loss in symptomatic patients is so low that no revascularization treatment could be considered “limb-sparing.”

Diabetes is a major predictor of outcome. Jonason and Ringqvist followed 224 nondiabetic patients and 47 diabetic patients over 6 years. Gangrene occurred in 31% of the diabetic patients, but in only 5% of those without diabetes. Diabetes has been associated with more than 50% of major amputations in patients with peripheral arterial disease.

Long-term survival is reduced in patients with iliofemoral obstructive disease as compared with the normal population. The risk of all-cause mortality in patients with large-vessel peripheral arterial disease compared with the normal population is increased approximately 3-fold, whereas the risk of cardiovascular death is increased 6-fold, but the most common cause of death in these patients is myocardial infarction or stroke.

Magnetic resonance angiography is an emerging noninvasive approach for imaging the peripheral circulation. It does not involve the risk of intravascular catheterization or conventional contrast agents. Invasive imaging with contrast arteriography, however, is still required when the diagnosis remains uncertain or when endovascular procedures are contemplated.

Peripheral interventions, either surgical or endovascular, have no impact on survival, but they can improve quality of life. Thus, indications for peripheral intervention in the setting of iliofemoral obstructive disease are largely related to the presence of symptoms and the potential impact of the symptoms for the affected individual. Progression of intermittent claudication to severe disabling symptoms, such as claudication after less than 200 meters, is a reason to consider surgical revascularization or angioplasty. The presence of rest pain or ischemic ulceration is a more compelling indication for revascularization. The indications for bypass reconstruction of the femoral-popliteal and femoral-tibial segments are generally more stringent than those for aortofemoral reconstruction, and likewise the indications for angioplasty of vessels below the knee are more stringent than those for iliofemoral intervention. It should be noted that preservation of inflow to the level of the profunda femoris is important for maintenance of collateral circulation to the infrapopliteal segment. In patients who present with claudication, however, there should never be a presumption that any revascularization strategy can save limbs.

Whenever a catheter-based or surgical approach is recommended, concomitant medical therapy must also be strictly enforced to prevent progression of disease. Patients who smoke
should be counseled emphatically about complete smoking cessation. Hypercholesterolemia must be brought under control with diet or statin therapy to achieve target low-density lipoprotein levels of less than 100 mg/dL. Hypertension must be controlled. Exercise and weight loss are also important. Although strict control of blood glucose in diabetics may influence the natural history of small-vessel disease, there are no data available that yet demonstrate a favorable impact on the progression of large-vessel lower-extremity arterial disease.

In addition to abrogating disease progression, certain medical therapies may also improve symptoms. The use of cilostazol (a type III phosphodiesterase inhibitor) and supervised exercise programs have all been associated with improvement in walking distance in patients with claudication caused by peripheral arterial disease. Preliminary data suggest a potential benefit of cholesterol lowering with atorvastatin, but the clinical significance of this remains unclear.

References


Concomitant Peripheral Arterial Disease and Coronary Artery Disease: Therapeutic Opportunities
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