Analysis of the Third National Health and Nutrition Examination Survey (1988 to 1994) suggests that chronic kidney disease (CKD) is a major public health problem (1). Approximately 11% of the US population has CKD. Roughly half have a GFR <60 ml/min per 1.73 m² with or without kidney damage (stages 3 to 4), and half have exclusively kidney damage as manifested by microalbuminuria (stages 1 to 2) (2). It is widely recognized that the prevalence of stage 5 CKD is also increasing at a rapid rate, and it is estimated that the number of patients who have ESRD may reach 2.24 million by 2030 (3).

Evidence to establish reduced GFR as an independent risk factor for cardiovascular disease (CVD) mortality has emerged. Analysis of data from several population-based epidemiologic studies (4,5) demonstrates poorer outcomes regarding stroke, myocardial infarction, and congestive heart failure (CHF) in patients with even mild compromise of kidney function. The morbidity of this group of patients constitutes an economic burden both directly in terms of resource utilization and indirectly through loss of productivity and impaired quality of life (2).

Atherosclerotic renovascular disease (ARVD) can result in renovascular hypertension. However, ARVD is an increasingly recognized cause of CKD (6,7). In this article, we focus mainly on ARVD or renal artery stenosis (RAS) secondary to atherosclerosis as a cause of ischemic nephropathy. ARVD is a disease of aging, and several studies have shown its strong association with extrarenal atherosclerotic disease (8–10). Patients with ARVD seem to be at a much greater risk for cardiovascular death than for progressing to renal replacement therapy (11). Whether renal revascularization can benefit renal and cardiovascular outcomes has not been established.

Prevalence

Atherosclerosis is the cause of approximately 90% of RAS in adults who are older than 40 yr (12). Overall, renal artery disease mirrors the extent and severity of atherosclerosis elsewhere in the circulation.

In autopsy studies, RAS has been found in 4 to 50% of patients, with a markedly increased prevalence among individuals who were older than 60 yr as compared with those who were younger than 60 yr (16.4 versus 5.5%). In contrast, significant ARVD has been shown in patients who underwent aortic angiography; RAS has been reported in 38% of patients with aortic aneurysm, 33% in those with aortic occlusive disease, and 39% in those with lower limb occlusive disease (13).

Most recent studies describe a prevalence of RAS of 14 to 29% in individuals with coronary artery stenosis and <10% in individuals with normal coronary arteries (14,15). One of the largest studies to evaluate the prevalence of RAS included 1305 consecutive patients who underwent coronary angiography. Significant unilateral (all ostial) and bilateral renovascular disease (≥50% diameter narrowing) occurred in 11 and 4%, respectively. Seventy percent of the patients had normal renal arteries, and 15% of patients were believed to have insignificant RAS (14).

The prevalence and the severity of RAS in patients who underwent cardiac catheterization and were deemed to be at risk for RAS on clinical or laboratory criteria have also been examined. Patients who exhibited at least one of four predefined selection criteria (severe hypertension, unexplained CKD, acute pulmonary edema with hypertension, or severe atherosclerosis) underwent diagnostic renal angiography. Renal angiography was diagnostic in 837 patients. Evident ARVD was present in 39% of the population, with RAS ≥50% in 14.3% and severe stenosis (≥70%) in 7.3% (16).

Patients with CHF constitute another group that is likely to have a high prevalence of ARVD. MacDowall et al. (17) showed the prevalence of ARVD in 86 elderly (>70 yr) patients who presented with CHF to one medical unit. The renovascular anatomy was defined by magnetic resonance angiography (MRA). Significant ARVD (RAS >50%) was present in 34% of 86 patients. Individuals with RAS had higher creatinine levels (2.8 versus 1.9 mg/dl) and more peripheral vascular disease (PVD) (31 versus 9%). Finally, claims data from a 5% random sample of the US Medicare population indicated an incidence of 3.7 per 1000 patient-years (11).

RAS as the cause of ESRD (rather than renal artery narrowing) is even less certain. RAS is cited as the cause of ESRD in 5 to 8% of patients (18). For example, over a 20-yr period in one hemodialysis unit, Mailloux et al. (19) reported an 11 to 15% incidence of ARVD among new patients with a median age of 70 yr (range 37 to 86 yr). Using the US Renal Data System
database, Fatica et al. (18) found an increased incidence of renovascular disease as the cause of ESRD (RVD-ESRD) from 2.9/10^6 in 1991 to 6.1/10^6 in 1997. The risk for RVD-ESRD correlated positively with older white men and negatively with black, Asian, and Native American race.

The true prevalence of ARVD is difficult to ascertain. No true study of the prevalence of RAS has been performed in an unselected population. Most studies have selected patients with some risk factors for RAS, such as coronary artery disease (CAD), peripheral vascular disease, diabetes, dyslipidemia, or hypertension (HTN). Another important reason for the lack of accurate determination of the prevalence of ARVD has been the need for a reliable definition (e.g., renal artery narrowing, HTN, loss of GFR, biopsy) as well as the diversity of the diagnostic methods used to determine the prevalence of the condition (17).

Pathogenesis

The cause of ischemic nephropathy is more complex than narrowing of the renal artery from atherosclerotic RAS (20). It is widely recognized that deterioration of renal function in the presence of RAS may not reflect “ischemia.” In addition, in azotemic patients with ARVD, other potential or contributing causes of CKD, such as obstructive uropathy, primary glomerular disease (suggested by heavy proteinuria), drug-related renal insufficiency, and uncontrolled HTN, should be excluded (20).

Metabolic requirements of the kidney are satisfied with <10% of blood flow. Therefore, decrements of renal blood flow (RBF) in the presence of anatomic lesions may not be sufficient to explain decrements in renal function (21). Furthermore, during reductions in renal perfusion pressure by up to 40%, RBF and GFR are maintained by autoregulation (22). Greater reductions of renal perfusion pressure are accompanied by steeper declines in GFR than RBF. A 40% decline in renal perfusion pressure occurs when the renal artery is narrowed by 70 to 80% (23). This degree of obstruction has been termed “critical stenosis” (24). Thus, in patients with atherosclerotic RAS, restriction of blood supply to the kidney does not induce atrophy and fibrosis simply by the lack of red cell and oxygen delivery (25).

Textor (26) proposed a sequence of events for chronic ischemic renal injury wherein repetitive episodes of renal hypoperfusion might produce irreversible parenchymal damage beyond a stenotic main renal artery lesion. The earliest consequence of renal underperfusion is an increase in renal with a proportional generation of angiotensin II (Ang II). Ang II promotes secretion of endothelin-1 in cultured mesangial cells, and renal vasoconstriction that is induced by endothelin-1 is linked to Ang II. Ang II increases expression of the TGF-β gene and of interstitial PDGF-B mRNA, thereby contributing to the build-up of extracellular matrix and collagen IV in the renal interstitium (25). Thus, multiple pathways, some of which depend on the activation of the rennin-angiotensin system, contribute to renal parenchymal damage.

Clinical Syndrome

Ischemic renal disease, or ischemic nephropathy, has been characterized as a clinically significant reduction in renal function as a result of compromise of the renal circulation (27). When RAS presents as ischemic nephropathy, the most common clinical syndromes are (1) unexplained renal insufficiency in the setting of HTN, (2) progressive azotemia in the setting of HTN, (3) azotemia in the setting of CAD or PVD, or (4) angiotensin-converting enzyme inhibitor (ACEI)-induced acute renal failure (ARF). Flash pulmonary edema is an unusual form of presentation for RAS (<10% of cases; Table 1).

ARF after the initiation of ACEI therapy is common in patients with hemodynamically significant bilateral ARVD. In the presence of hemodynamically significant ARVD, GFR is preserved by two autoregulatory mechanisms: Afferent arteriolar vasodilation and efferent arteriolar vasoconstriction.

Ang II that is produced by the intrarenal generation of renin as a result of renal hypoperfusion is postulated to maintain efficient arteriolar tone. Ang II–mediated efferent arteriolar vasoconstriction maintains glomerular capillary pressure and GFR (28).

In the setting of RAS, ACEI block Ang II formation, and angiotensin receptor blockers (ARB) prevent Ang II action. These effects blunt autoregulation mechanisms and decrease GFR. The effects of ACEI and ARB differ on unilateral comparison with bilateral renal artery disease. Van de Ven et al. (29) demonstrated that in patients with severe bilateral RAS, ACEI resulted in an increase of at least 20% in the serum creatinine. The decrements in glomerular filtration that are induced by ACEI usually occur within the first few days of starting therapy. However, the Dutch group reported that whereas 38% of patients have a decline of GFR at 4 d, 80% of patients experience some decrement in GFR at 31 d.

In hypertensive patients in whom 2 wk of ACEI therapy had no significant effect on serum creatinine, addition of diuretics (furosemide) resulted in a significant increase (>20%) in the plasma creatinine in 12 of 15 patients. These results indicate that plasma creatinine concentration should be measured at 4 and 31 d after initiation of ACEI or ARB, especially in the setting of diuretic use in patients who are at high risk for RAS.

The Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease recommend that a reduction in GFR of >30% from baseline after ACEI or ARB therapy should be considered suggestive of occult RVD. When other causes of acute increases in creatinine are not identified, discontinuation of the ACEI or ARB is recommended (30). No recommendations are given regarding the timeline for evaluat-

<table>
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<th>Table 1. Clinical presentation of ischemic nephropathy</th>
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<td>Unexplained renal insufficiency in the setting of HTN</td>
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<td>Progressive azotemia in the setting of HTN</td>
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ACEI, angiotensin-converting enzyme inhibitor; ARF, acute renal failure; CAD, coronary artery disease; HTN, hypertension; PVD, peripheral vascular disease.

a
ing serum creatinine after ACEI or ARB therapy is started in patients who are at high risk for ARVD.

Because ACEI and ARB alter glomerular hemodynamics rather than RBF, ACE inhibition–induced reduction in glomerular filtration almost always improves after discontinuation of therapy. The effect in unilateral renovascular disease is slight because of equivalent increases in glomerular filtration in contralateral kidneys.

Although proteinuria has been recognized as an important predictor of progression in diabetic nephropathy (31), in some studies, the risk for progression of renal disease by proteinuria is as great in patients without diabetes as it is in those with diabetes (31). Proteinuria, including nephrotic-range proteinuria, has been reported in patients with ARVD, although in most cases, the proteinuria is mild (32,33). Makanjuola et al. (34) surveyed 94 patients who were followed by two renal centers that were interested in ARVD. Fifty-two percent of the patients had proteinuria. In patients with GFR ≥50 ml/min mean urinary protein excretion was 400 mg/24 h, and in patients with GFR <50 ml/min proteinuria ranged from 500 mg/24 h to 2.4 g/24 h. In this series, proteinuria was recognized as a marker of severity of parenchymal disorder in atherosclerotic nephropathy. Because renal parenchymal disease rather than RAS alone may be a better predictor of progression to ESRD (see below), proteinuria is an important finding in patients with RAS. The mechanism for the proteinuria may be the high intrarenal level of Ang II. Correction of the stenosis, which lowers Ang II levels, leads to an amelioration of the proteinuria (32,33).

Natural History

The natural history of RAS includes renal failure progression and decreased overall survival. Because renal artery occlusive disease can result in loss of renal mass, the challenge is to intervene at a stage when ischemic changes are reversible or perhaps before parenchymal injury has occurred. The exact relationship between the degree of renal artery narrowing and the risk for subsequent loss of renal mass is not known. One of the major difficulties in understanding the natural history of RAS is that consistent end points by which to define progression have not been identified (35). A number of surrogate end points have been used, including decrease of renal artery diameter, decline in GFR, and renal atrophy.

Anatomic Progression (Renal Artery Diameter)

It seems that progression is dependent on the extent of initial lesions, time of follow-up, methods used to study renal artery diameter, and indications for the initial study. When defined as >25% decrease in luminal diameter, rates of progression of renovascular disease vary between 25 and 75% over mean follow-up periods that range between 2 and 5 yr (36). The incidence of complete occlusion ranges from 8 to 16%. Renal artery occlusion tends to occur in renal vessels, with baseline stenoses exceeding 60%, especially in patients with bilateral disease (36).

Crowley et al. (37) describe RAS progression in 1189 patients who underwent cardiac catheterization. Mean time between cardiac catheterizations was 2.6 yr. Significant disease (>50% of renovascular disease) was present in 2.4% at baseline and 13.5% at follow-up. New renovascular disease or progression of existing disease occurred in 133 (11.1%) patients at follow-up. Factors that were identified as predictors of disease progression were female gender, age, CAD, HTN, and renovascular disease at baseline. In contrast, Caps et al. (35) reported that in patients in whom progression of RAS was monitored with serial renal artery duplex scans, the 3-yr cumulative incidence of renal artery narrowing stratified by baseline RAS severity was 18, 28, and 49% for renal arteries that initially were classified as normal, <60% stenosis, and ≥60% stenosis, respectively. The risk for progression to complete renal artery occlusion was low (only nine renal arteries), which is in agreement with other published studies. In this study, renal artery disease progression was defined as either an increase in the renal artery peak systolic velocity of ≥100 cm/s compared with the baseline examination or renal artery occlusion. Comparison of these two important studies illustrates the problems related to different study designs with regard to population cohort, different imaging methods, and different indication for screening.

Functional Progression (GFR)

Loss of GFR may be a more useful end point for progression of ischemic nephropathy. However, there does not seem to be a tight relationship between renal artery diameter and loss of GFR.

Leertouwer et al. (38) compared the need for renal replacement therapy in patients who had untreated RAS with ≥50% stenosis with control subjects who did not have RAS and were matched for age and gender. RAS was identified in 126 of 386 patients evaluated. None of these patients required renal replacement therapy during 10 yr of follow-up. Serum creatinine levels, although 20% higher in patients with RAS compared with control subjects, remained stable during the follow-up. Chabova et al. (39) reported follow-up data on 68 patients with “incidental” RAS (>70% stenosis). These patients underwent angiography for indications other than for suspicion of renovascular disease (e.g., PVD) and were treated without revascularization for >6 mo. The time to last follow-up averaged 39 mo. Clinical progression that led to renal insufficiency or revascularization developed in <12%. Many (58%) of the patients had serum creatinine levels <1.3 mg/dl and only moderate HTN. The authors attributed the low rates of deterioration of renal function summarily to adequate BP control (<140/90 mmHg).

In a further study of 71 patients with atherosclerotic RAS, Suresh et al. (40) reported that the severity of proximal RAS is often unrelated to the severity of renal dysfunction. Lumen diameters were classified from <25% of normal to >60% of normal. Renal impairment was equally decreased in patients with mild proximal renovascular disease as in those with severe narrowing of diameter or in patients who had unilateral renal artery occlusion. Similarly, Cheung et al. (41) assessed time to progression to ESRD in patients with unilateral atherosclerotic renal artery occlusion and contralateral insignificant (<50%) or significant (>50%) RAS. Dialysis-free survival was reported in 142 patients. Irrespective of whether the nonoc-
cluded artery was normal or had stenosis of varying significance, time to renal replacement or death did not correlate with renovascular anatomy. Paradoxically, the Cox hazard analysis for risk for ESRD or death indicated that insignificant RAS was more of a risk (odds ratio 3.39) than more significant RAS (odds ratio 0.95). It is not easy to account for these observations (Figure 1).

The most likely explanation is that GFR losses in RAS are not determined primarily by the proximal large vessel lesion. Rather, decreases in GFR correlate better with parenchymal damage downstream of the lesion. Parenchymal injury is multifactorial in origin from cholesterol emboli, longstanding HTN, and ischemia. This explanation is further supported by the observation that repair of RAS does not result uniformly in stabilizing GFR. This observation would be expected if more distal renal factors were present.

Renal Atrophy

Reduction in kidney size or atrophy may be a better indicator of progression of ARVD. As much as renal atrophy can be attributed to lack of blood flow, changes in kidney size should be a reasonable outcome measure of the effect of reduction of blood flow. Relatively few reports in the literature deal with the problem of decreasing kidney size in patients with RAS.

In a study by Dean et al. (42), changes in renal function were evaluated in 41 patients who had renovascular HTN and were followed from 6 to 84 mo on medical treatment. A decrease in kidney size >10% was noted on serial intravenous pyelograms in 37% of patients, and GFR dropped between 25 and 50% in 12 patients. Schreiber et al. (36) examined retrospectively kidney length changes that were associated with arteriographic progression of renal artery disease. Decrease in kidney size was defined as a >1.5-cm difference in pole-to-pole measurements on serial x-rays. Forty-four percent of patients with atherosclerotic RAS demonstrated disease progression, and 70% of these patients showed significant decreases in kidney size. Caps et al. (43) evaluated the incidence and risk factors for renal atrophy among kidneys with atherosclerotic RAS. Renal atrophy was defined as a reduction in renal length of >1 cm. A total of 204 kidneys in 122 patients were followed for a mean of 33 mo. The 2-yr cumulative incidence of renal atrophy was 5.5, 11.75, and 20.8% in kidneys with baseline renal artery classified as normal, <60% stenosis, and ≥60% stenosis, respectively.

Wright et al. (44) investigated the impact of histologic changes on renal functional outcome in a small group of patients whose renal biopsies were compatible with ischemic or atherosclerotic nephropathy, irrespective of whether significant ARVD had been demonstrated at angiography. They found a tight relationship between decreases in creatinine clearance (CrCl) over time and renal damage score from biopsy samples. It would be reasonable to presume that the extent of fibrosis and sclerosis seen on kidney biopsy may be a helpful predictor of progression, although the reality is that biopsies are rarely performed in these patients.

In summary, although data are limited, the best predictors of progression to ESRD in patients with ARVD seem to be baseline GFR and renal atrophy. Renal artery diameter is not as helpful. Careful studies to compare each of these variables are needed.

While the relationship between RAS and progressive GFR loss is controversial, of more significance is the relationship between RAS and survival. Conlon et al. (45) reported that in patients who underwent cardiac catheterization, 4-yr survival was 86% in those without RAS and 65% in those with RAS. In additional studies, they reported that the extent of RAS also influenced survival. In patients with RAS <75% of diameter, 4-yr survival was 89%, whereas in those with ≥75% narrowing survival was 57% (46). The major cause of mortality is ischemic heart disease and CVD.

In patients with ESRD, survival during renal replacement therapy seems to be poor. Mailoux et al. (19) reported a 25-mo median survival and 5- and 10-yr survival rates of 18 and 5%, respectively, in patients who required hemodialysis secondary to ARVD. This compares to a 133-mo median and 77% 5-yr and 59% 10-yr survival in patients with polycystic kidney disease.

It has become clear that many patients with CKD do not reach ESRD. Rather, survival is negatively affected by a striking increase in CVD. Whether cardiovascular events are more common in RAS compared with other forms of CKD is unknown. However, it is clear that adverse cardiac event rates exceed those of the general population: Atherosclerotic heart disease, four-fold; PVD, five-fold; CHF, almost four-fold; cerebrovascular accident or transient ischemic attack, three-fold (11).

Diagnosis

The evaluation of patients who are suspected of having ischemic nephropathy requires a series of tests to define the presence of one or two functional kidneys, the size of both kidneys, and an accurate delineation of the vascular anatomy. Demonstration of a vascular lesion is not always proof of functional significance of the lesion. Additional tests are required to establish whether the atherosclerotic renovascular lesion is responsible for a clinically meaningful decrement in GFR (7).
Although many similarities exist between the diagnostic evaluation of patients with presumed ischemic renal disease and that of patients with suspected renovascular HTN, it is important to note that there is a fundamental difference between these diagnoses. Renovascular HTN is most commonly associated with at least one normally functioning kidney, and ischemic renal disease often involves significant dysfunction of both kidneys (7).

Tests of structural abnormalities in the renal arteries include conventional angiography, spiral computed tomography (CT) angiography, and MRA. Tests that demonstrate functional abnormalities secondary to RAS are renal-vein-renin measurement, ACEI renography, and color Doppler sonography.

Renogram after ACEI

The principle of this test is based on the role of Ang II in maintenance of GFR in patients with physiologically significant RAS. Ang II maintains efferent arteriolar tone, pressure in the glomerulus, and glomerular filtration pressure. Administration of ACEI decreases efferent tone. In the presence of fixed lesions in the main renal artery, pressure in the glomerulus and GFR decreases. Oral captopril (25 to 50 mg) is given 1 h before the isotope-tagged compound is injected. In unilateral RAS, ipsilateral decrements in GFR are usually accompanied by corresponding increases in glomerular filtration in contralateral kidneys as a consequence of elimination of Ang II–mediated vasoconstriction. The net result is that disparities between GFR in the two kidneys are enhanced. Markers of glomerular filtration, such as 99mTc-diethylenetriamino-pentaacetate, or compounds that are secreted by the proximal tubule, such as 125I-orthiodihippurate and 99mTc-mercaptoacetylglycylglycylglycine, have been used. The latter may be more reliable in patients with renal insufficiency. The value of ACEI renography has been questioned in patients with reduced renal function because basal renography is abnormal in patients with impaired renal function. Further reductions in GFR after ACEI may not be identifiable (47). In patients in whom renal function is slightly or moderately reduced (e.g., GFR >50 ml/min), some studies have demonstrated a high sensitivity with regard to RAS (87% [48] and 86% [49]). Erbsloh-Moller et al. (50) showed significant prolongations of residual cortical activity after renography in patients with RAS and serum creatinine values >1.8 mg/dl, compared with patients with the same degree of reduction in renal function without RAS. However, other studies have reported the sensitivity to be as low as 75% (51). In summary, ACEI renography may be an effective screening method for RAS in patients with normal renal function as well as in patients with GFR as low as 50 ml/min. The advantage of ACEI renography is that the test assesses the functional significance of RAS independent of anatomy. A limitation of the test is that it requires careful patient preparation (ACEI and ARB should be discontinued).

Doppler Sonography

Ultrasound is used to determine kidney size. Differences in size of >1.0 cm (in the absence of other renal diseases) suggest the likelihood of renovascular disease. However, the sensitivity of this finding is low. Duplex sonography provides information regarding blood flow in the main renal arteries and in intrarenal vessels (52). The intrarenal resistive index (RI), calculated from the signals of the segmental arteries, can be valuable in detecting renal fibrosis and/or atrophy in patients with renovascular disease. Ike et al. (53) showed a direct relationship between RI and histopathologic characteristics, particularly arteriosclerosis. Furthermore, greater RI at renal biopsy is related to progressive renal impairment. In a recent study, renal RI values of 0.80 or greater reliably identified patients who had RAS and in whom revascularization with angioplasty or surgery did not improve renal function, BP, or kidney survival (52). Doppler sonography also has been used to identify the location of a RAS. However, several problems have emerged with the use of direct analysis of flow in the stenotic segment: (1) The method demands optimal sonographic test conditions and is limited by patient obesity and by intestinal gas overlying the area of interest, (2) the examination time is long even with experienced staff, and (3) accessory arteries and aberrant arteries can rarely be detected. These problems account for the considerable disagreement over sensitivity, specificity, and predictive values in the use of Doppler sonography of the renal vasculature to screen for RAS (47). Spies et al. (54) reviewed 18 studies of RAS by duplex sonography from the 1980s to the early 1990s. The sensitivity was from 63 to 100% and the specificity was from 73 to 100% for detecting a RAS. An advantage of Doppler sonography is that the sensitivity and the specificity are not dependent on glomerular filtration. Therefore, in centers with considerable experience, Doppler sonography is an acceptable alternative to ACEI renography in screening for RAS.

Spiral CT Angiography

This test is a reliable and accurate screening for evaluation of renal arteries in patients with suspected ARVD (55). In detecting RAS of >50%, spiral CT angiography has been reported to have sensitivity of 64 to 99% and specificity of 92 to 98% (47,56). The most important advantage of spiral CT angiography compared with conventional angiography is the visualization of both the arterial lumen and the arterial wall (which could be calcified). The risk for nephrotoxicity seems to be similar to conventional angiography (47).

MRA

This technique is the initial screening test for the diagnosis of RAS in patients with reduced renal function and in patients with allergy to iodinated contrast agents. The test is performed by injecting a bolus of a gadolinium chelate and scanning with a three-dimensional volumetric data collection sensitized to the T1 shortening effects of gadolinium (57). Gadolinium-enhanced MRA has been proved to have a high sensitivity for detecting stenosis in main and accessory renal arteries (55). One series evaluated 37 patients who had HTN and underwent both MRA and arteriography. Using the renal arteriogram as the gold standard, MRA had a sensitivity of 100% and a specificity of 96% for the detection of stenosis of the main renal arteries (58). Schoenberg et al. (59) reported that a combined morphologic
and functional magnetic resonance examination decreased interobserver variability and offered reliable grading of RAS on the basis of stenosis morphology and hemodynamic changes.

The Renal Artery Diagnostic Imaging Study in Hypertension (RADISH) Study Group found a combined sensitivity an specificity of only 62 and 84%, respectively, for the finding of atherosclerotic stenoses of 50% or greater in patients who had HTN and were suspected of having RAS (56).

MRA with gadolinium as contrast has the advantage that it can be performed independent of impairment of GFR and does not require iodine. The limitations of the test is that it provides anatomic rather than physiologic information and has limited power to assess intrarenal arteries.

**Renal Arteriography**

Despite the risks of contrast nephropathy and atheroembolic renal disease, arteriography has been considered to be the gold standard diagnostic test. The significant morbidity associated with the renal arteriogram has made this diagnostic tool unappealing as a screening test, specifically in an aging population with a growing list of comorbidities.

In summary, with regard to the diagnostic evaluation of patients with suspected RAS:

1. The choice of the diagnostic test is center dependent (local experience and equipment). Probably the best test is the one performed most often at individual facilities.
2. In patients with a GFR >50 ml/min, the first test should be a functional study (e.g., ACEI renography).
3. In patients with a GFR <50 ml/min, the first test should be an anatomic study (e.g., MRA).
4. Finally, it is important to recognize that with the possible exception of the finding of kidneys <7.0 cm, these tests do not predict who will benefit from reperfusion. Although the results from studies of RI are exciting, results to date are from a single publication (52).

The role of “screening” renal angiogram during coronary angiography continues to be debated vigorously.

Arguments in favor of “drive by” angiography include:

1. RAS is a prevalent comorbid condition in cardiologic practice, because the risk factors for CAD and ARVD are identical. The renal angiogram followed with angioplasty/stent deployment of ostial renal artery lesions can be performed effectively with equipment adapted for coronary interventions (60).
2. In patients who undergo cardiac catheterization, RAS is an independent risk factor for mortality, which correlates with the severity of the ARVD (46).
3. RAS causes or aggravates HTN and/or interferes with its treatment, which has a negative impact on the primary and secondary prevention of coronary heart disease (60).
4. CKD from ischemic renal disease impairs the outcome of coronary artery bypass grafting and percutaneous interventions (60).

Arguments against performing routine screening renal arteriogram include:

1. The anatomic demonstration of a lesion in the renal arteries is not absolute evidence for the functional significance of such lesion. Thus, renal artery diameter does not correlate with GFR or progression of GFR (61).
2. HTN can be treated safely and effectively with antihypertensive drugs in most patients with RAS (60).
3. The preservation of renal function through interventional treatment of ARVD is less certain.
4. The procedure has definitive risk of worsening renal function through contrast-induced ARF and/or atheroembolism. Therefore, endovascular interventions carry definitive risk that should weigh against the likely benefits.

In the absence of prospective data on which patients would benefit (or those at high risk), on the basis of existing evidence, we do not believe that routine screening of the renal artery during coronary angiogram is warranted.

**Treatment**

Despite extensive research and opinion on this topic, there remains a great deal of controversy concerning the appropriate management of RAS in ischemic nephropathy. It is important to realize, depending on the clinical syndrome and the extent of atherosclerotic burden, that patients with ARVD may have very different prognoses and responses to therapy (62). Although revascularization “makes sense,” the beneficial effects of revascularization are often less than anticipated. In considering revascularization (angioplasty with/without stenting or surgery), the end points studied have been renal artery patency, BP control, CKD progression, and mortality. Interpretation of data is complicated by comorbidities, including CAD, CHF, cerebrovascular accident, CKD, diabetes, etc. Aside from a small study (63), no randomized, prospective studies have indicating that revascularization decreases mortality. Most likely, this results from the fact that most patients have extensive atherosclerotic burdens that outweigh the effects of RAS on CVD. Furthermore, no randomized, prospective studies support the conclusion that revascularization slows progression of CKD.

The effects of revascularization on BP and renal artery patency have been compared with medical therapy alone. The largest randomized trial to date to compare medical management with angioplasty in ARVD is the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) trial (64). Inclusion criteria were HTN uncontrolled by two drugs and atheromatous stenosis of at least 50% documented on angiography. A total of 106 patients were randomly assigned (56 to angioplasty and 50 to medical treatment). Three months after randomization, BP were the same in the two groups, although the angioplasty patients were taking significantly fewer medications and also had higher average CrCl. Nearly half (22 of 50) of the medically treated group had to undergo subsequent angioplasty. These 22 patients showed a significant improvement in BP and no change in CrCl. At 12 mo, there were no differences in BP control or renal function. The DRASTIC investigators concluded that angioplasty had little advantage over medication in the treatment of ARVD, unless HTN was refractory to medical management or there was progressive azotemia.
Percutaneous transluminal angioplasty (PTA) has been compared with angioplasty with stent placement (PTAS) as well. Forty-two patients with ARVD received PTA and 43 patients received PTAS. The primary success rate was 57 and 88% in those who received PTA and PTAS, respectively. Although the patency at 6 mo was greater with PTAS (75 versus 29%) and restenosis rate was less with PTAS (14 versus 48%), the effects on BP (59 versus 49%) and GFR (approximately 60% stable or increase) were the same. Importantly, the complication rate of the procedure was consequential (43% PTAS, 39% PTA) (65). Studies that have compared revascularization with interventional radiology versus surgical procedures are unavailable.

Two types of surgical procedures have been used in RAS: Surgical revascularization to bypass the stenotic section and nephrectomy of small kidneys with relatively complete arterial occlusion. Revascularization is usually recommended for lesions that are localized in the distal segment of the renal artery. The mortality and the morbidity that are associated with this procedure depend on the severity of the PVD, extent of surgery required, underlying comorbidities, and the experience of the vascular surgeon. Interventional radiologic and surgical procedures have been less successful in the treatment of progression of renal failure than had been anticipated. The study by Rademacher et al. (52) suggested that the success of these procedures is dependent on the extent of downstream renal parenchymal injury rather than vascular stenosis. When the RI was >0.80 (an excellent indicator of nephrosclerosis or glomerulosclerosis), little benefit was seen with interventional radiology or surgery. In this study, 35 patients with an RI of at least 0.80 and 96 patients with an RI of <0.80 underwent revascularization. In the patients with an RI >0.80, the mean arterial pressure did not decrease by 10 mmHg or more (97% patients) and renal function declined (decrease in CrCl of at least 10%) in 28 patients (80%). Among patients with an RI <0.80, the mean arterial pressure decreased (>10%) in 90 patients and renal function worsened in only three patients.

In addition to the predictive effect of RI, data indicate that patients with recent loss of GFR are more apt to benefit from revascularization as well. Murray et al. (66) studied 59 patients who underwent PTA. Renal function improved in 58% of patients. The authors concluded that the slope of the reciprocal serum creatinine plot before PTA was significantly associated with favorable changes in progression rate after PTA.

In summary, in the absence of prospective data and of consensus statements, we use the algorithm in Figure 2 for treating patients with RAS and suspected ischemic nephropathy. Revascularization should be considered in RAS with rapid worsening of renal function or resistant HTN (four or more antihypertensive agents especially in the setting of CHF or recurrent flash pulmonary edema). When the kidney size is <8.0 cm long (67) or the RI is ≥0.80 (52), there is little chance of BP improvement or recovery of GFR. Summarized in Table 2 are predictors of kidney salvageability. Renal arteriography is a requirement for precise localization of the stenotic lesion. PTA is the initial procedure of choice. However, as noted, angioplasty is usually inadequate (64). Stent placement is required when there is elastic recoil with a residual stenosis of 30% or more. This occurs more commonly in ostial than in truncal lesions. Therefore, most radiologists recommend primary stent placement for lesions within the aortic wall or within 10 mm of the aortic lumen (68). Vascular intervention in ARVD is associated with an increase risk for developing worsening kidney function soon after revascularization procedures (69,70). Outcomes in patients in whom complications are reported are uniformly worse. Some investigators have reported that >35% of patients require renal replacement therapy and accelerated mortality (71).

**Future Directions**

Although the algorithm presented in Figure 2 is reasonable, others would find it too aggressive or too conservative. At the base of this dispute lies the uncertainty of both the benefits and the risks posed by manipulation of the renal arteries (72). Clear guidelines are not available because of the lack of sufficient prospective, controlled data. The Cardiovascular Outcomes in Renal Artery Lesions (CORAL) trial, will examine the effects of medical therapy alone or medical therapy plus stenting of atherosclerotic RAS (72). The primary end point in CORAL is a composite end point, defined as “event-free survival” from
cardiovascular and renal adverse events. Other studies with similar outcomes to the CORAL trial have been initiated (73). Even after the results of these studies are made available, clinicians will find the risk–benefit ratio of intervening on patients with ARVD challenging. Other major areas of clinical research that are needed in ischemic nephropathy are:

- Study of the prevalence in age-adjusted subgroups (e.g., ischemic heart disease, CHF, proteinuric and nonproteinuric CKD);
- Studies on the natural history of RAS and ischemic renal disease;
- Diagnostic markers that will allow accurate detection of initiation and stage of kidney injury;
- Analysis of pre-existing factors that predict benefit or risk of stenting.

Conclusion

Ischemic nephropathy secondary to renovascular disease is common. The renal dysfunction and worsening GFR that are observed in patients with ARVD result from RAS and distal parenchymal disease. The prevalence of ischemic nephropathy seems to be increasing in the aging population. The natural history of RAS and measures to detect accurately progression of kidney disease are not certain. Identifying patients who are at risk for progression of CKD as well as those who will benefit from intervention remain elusive goals that should be addressed by prospective trials. Whether some of these issues will be addressed with refined imaging methods or functional studies is not yet established. Currently, optimal treatment remains vague and should be adapted to individual patient’s clinical presentation as well as comorbidities.

References


