Ischemic Nephropathy: Where Are We Now?

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Abstract. Identification and reversing the loss of kidney function beyond occlusive disease of the renal arteries poses a major clinical challenge. Recent studies indicate that atherosclerotic renal artery stenosis develops as a function of age and is commonly associated with other microvascular disease, including nephrosclerosis and diabetic nephropathy. The risks of renal artery stenosis are related both to declining kidney function and to accelerated cardiovascular disease, with increased morbidity and mortality. Newer drugs, including agents that block the renin-angiotensin system, have improved the level of BP control for renovascular hypertension. Progressive renovascular disease during medical therapy can produce refractory hypertension, congestive heart failure, and renal failure with tubulointerstitial fibrosis. Recent studies indicate a complex interplay of oxidative stress, endothelial dysfunction, and activation of fibrogenic cytokines as a result of experimental atherosclerosis and renal hypoperfusion. Advances in imaging and interventional devices offer major new opportunities to prevent progressive loss of kidney function. Recent series indicate that although 25 to 30% of patients with impaired renal function can recover glomerular filtration after revascularization, many have no apparent change in kidney function and 19 to 25% experience a significant loss of kidney function, in some cases as a result of atheroemboli. To select patients who are most likely to benefit from vascular intervention, clinicians should understand the pathophysiology of developing ischemic nephropathy and the potential hazards of revascularization in the setting of diffuse atherosclerotic disease. Further research should be directed toward identification of critical disease, regulation of fibrogenesis, and the interaction with other atherosclerotic processes.

Few topics provoke more controversy between nephrologists and interventional cardiologists than management of atherosclerotic renovascular disease, particularly in the context of “ischemic nephropathy.” Although it long has been recognized that renovascular disease can initiate or accelerate hypertension, the role of renal artery disease as an important contributor to renal failure is a concept emphasized mainly since the 1980s (1). Some have proposed that this is a disease entity that may be “overlooked” (2), particularly with advances in the medical treatment of renovascular hypertension (3). Recent advances in vascular intervention make identification of a stenotic lesion an invitation for angioplasty or stenting. Occasionally, patients who experience major recovery of renal function after renal revascularization provide “proof of concept” that large-vessel occlusive disease can be an important cause of renal dysfunction. The controversy derives primarily from the difficulty in balancing the clinical benefits against the considerable risks of vascular intervention for individual patients.

The term “ischemic nephropathy” itself warrants precise definition. For the purposes of this article, “ischemic nephropathy” is taken to mean impairment of renal function beyond occlusive disease of the main renal arteries. It should be emphasized that deterioration of renal function does not necessarily reflect true “ischemia.” Because a major function of the kidney is filtration, blood flow to the kidney provides a vast oversupply of oxygenated blood per se. Less than 10% of the blood flow is needed for metabolic requirements of the kidney (4). Some authors prefer the term “azotemic renovascular disease” to avoid the supposition that loss of renal viability is necessarily related directly to impaired oxygenation (5).

Certainly, some patients develop ESRD with no identified renal disease other than atherosclerotic renal artery stenosis (RAS). Recovery of function after renal revascularization sometimes can free patients from dependence on dialysis. An example of such a patient is illustrated in Figure 1. A flurry of enthusiasm in the early 1990s for identifying such patients and for subjecting them to revascularization procedures produced disappointments, however. Reports of both surgical and endovascular revascularization for patients with advanced renal failure provide mixed messages. Whereas some patients obtain a major benefit, others experience either loss of renal function or major morbidity (5). Even recent reports offering “delayed dialysis” concede that risks of deterioration were substantial (17.9%) as was subsequent mortality (10.7%) (6). Particularly when severe aortic disease is present, attempts at revascularization can produce systemic atheroemboli, sometimes with catastrophic results. As a result, many nephrologists have become more conservative regarding vascular intervention than before.

This is a rapidly evolving field, in both clinical and experimental aspects. Developments in vascular imaging, including magnetic resonance angiography, Doppler ultrasound, and nontoxic contrast angiography (e.g., with gadolinium) make the identification of atherosclerotic stenoses more readily pos-
The demographics of patients who are identified with high-grade lesions are changing dramatically in favor of older ages and more severe comorbid disease risk. Tools for effective restoration of blood flow beyond stenotic lesions, particularly since the introduction of endovascular stents, make this a field of greater interest to cardiologists and interventional radiologists than ever before. One result of these developments is a changing role of the nephrologist, who may be asked to see patients only after the diagnosis and intervention for ischemic nephropathy has taken place. In some cases, joint consideration of the pros and cons of revascularization is undertaken as a collaborative effort beforehand. It behooves clinical nephrologists to have an appreciation of the risks and benefits of this condition, an understanding of the pathophysiologic basis for the loss of kidney function, and a thoughtful perspective on timing of renal intervention. This article summarizes our current understanding of the prevalence, pathophysiology, and natural history of this disorder and emphasizes areas that need further clarification.

Epidemiology of Atherosclerotic Renal Artery Disease

Atherosclerotic disease of the renal arteries is common. Many lesions of the renal artery occur in ostial segments and represent extension of adjacent aortic atherosclerotic plaque. The prevalence of such lesions is a function of both age and atherosclerotic risk factors in Western societies, including smoking, hypertension, dyslipidemias, and diabetes (7). Recent series of patients who were screened for the DRASTIC study reemphasize the predictive value of clinical variables, including age, symptomatic vascular disease, elevated cholesterol, and the presence of an abdominal bruit, as the most powerful predictors of detecting lesions of at least 50% vessel occlusion (8). The authors developed a scoring system with which one could estimate the pre-angiographic probability of finding such a lesion with accuracy at least equal to radionuclide angiography. How often renovascular disease leads to advanced renal failure, e.g., ESRD, is controversial. Studies of patients who are referred with chronic kidney disease indicate that vascular lesions can be detected commonly (ranging from 3.2% of patients under age 59 to 25% of those above age 70 (9)). Recent surveys of older subjects who were treated with dialysis indicate that vascular disease is now more commonly assigned as the cause of renal failure (2.1% in 1997 versus 1.4% of all ESRD cases in 1991), although this is a highly subjective diagnosis (10,11). Whether early vascular intervention would reduce the rate of progression to ESRD in such patients has not been demonstrated in a prospective, controlled manner.

A recent population-based study of >800 free-living subjects who did not have recognized kidney disease, lived in North Carolina, and were older than age 65 (mean age, 77.2 yr) indicated that renovascular disease of >60% lumen occlusion (as identified by careful Doppler ultrasound measurement) was present in 6.8%. It was more common in men than in women (9.1 versus 5.5%; P = 0.053) and related to age, HDL cholesterol, and increased systolic BP (12). The prevalence did not differ between black and white participants.

When patients who undergo coronary angiography are subjected to a screening aortogram, the prevalence of “high-grade” stenoses rises to 19 to 24%, particularly in those with hypertension and definite coronary disease (13,14). A subset of these subjects have bilateral disease (7% (14)). Patients with widespread peripheral arterial disease affecting the aorta and/or lower extremities have even higher rates of identified disease ranging between 35 and 50% of subjects as has been reviewed elsewhere (7,15,16).

Overall, renal artery disease mirrors the extent and severity of atherosclerosis elsewhere in the circulation. For this discussion, several important corollaries to this observation warrant emphasis. (I) Deterioration of kidney function attributable to
“ischemic nephropathy” is limited to those with renal artery disease affecting the entire renal mass (either bilateral arterial disease or disease to a solitary functioning kidney). Reduction in GFR for patients with unilateral renovascular disease suggests other parenchymal disease in the contralateral kidney and rarely improves after renal revascularization (17). The presence of RAS predicts subsequent mortality, regardless of whether renal revascularization is pursued (18). Mortality in patients with renovascular disease is related to cardiovascular events, including myocardial infarction, stroke, congestive heart failure, etc (19). Although progression of renal arterial disease leading to either total occlusion and/or irreversible renal injury can occur, the benefits of vascular repair must be considered in the context of other comorbid disease. Follow-up studies of “incidental” renal artery stenosis in patients with either coronary or peripheral arterial disease rarely identify progression to renal insufficiency but instead identify high rates of cardiovascular mortality (20).

Taken together, these data establish that RAS is highly prevalent, particularly in older patients with hypertension and other atherosclerotic disease. In many patients, it is an incidental finding. Understanding and identifying when stenosis participates in renal dysfunction distal to the lesion is the central issue.

Pathophysiology of “Critical” RAS and “Ischemic Nephropathy”

Hemodynamic studies across stenotic lesions indicate that pressures gradients and changes in blood flow can be detected only when lumen occlusion exceeds nearly 70 to 80% of luminal area. This degree of obstruction has been termed “critical” stenosis (21). Reduction of systemic arterial pressures proximal to critical lesions thereby induces hypoperfusion to the distal arterial segment, sometimes below levels needed for autoregulation of blood flow. Reduction of perfusion pressure to the kidney invariably activates pressor mechanisms to restore renal perfusion, including activation of the renin-angiotensin system, adrenergic stimuli, and other mechanisms (22). Further occlusion again reduces perfusion to the renal circulation and triggers a repeat cycle of elevation of systemic pressures. Unless interrupted, this sequence ultimately produces malignant-phase hypertension (23).

In clinical settings, antihypertensive therapy is directed at lowering systemic pressures to achieve proven benefits in reducing cardiovascular morbidity. The price of these benefits for patients with renovascular disease may be underperfusion of the poststenotic kidney(s). This can develop during therapy with any antihypertensive agent and can produce a loss of GFR when perfusion pressures fall below those needed for autoregulation (24). Revascularization of the kidney can remove the pressure dependence of GFR in such patients (21,25).

The above sequence has been studied most extensively when renal artery lesions are severe. Whether less severe disturbances in flow and shear stress to the vessel wall predispose to subtle alterations in intrarenal hemodynamics is less understood. Recent studies suggest that alterations of blood flow develop in an exponential manner at less severe occlusion (26). The precise pathways by which alterations in renal vessels induce tissue injury in the kidney are not well understood. Remarkably, fibromuscular disease (FMD) rarely produces renal failure despite producing sufficiently severe hemodynamic effects to activate systemic pressor mechanisms within the kidney. Disturbances of endothelial function (as studied in the forearm) develop with either FMD or atherosclerosis, which are reversible after successful angioplasty (27). FMD most commonly appears in younger women and is identified in the absence of other microvascular disease, e.g., dyslipidemia and diabetes. Conversely, loss of glomerular filtration develops almost exclusively for patients with atherosclerosis, which develops gradually superimposed on vascular changes related to aging, essential hypertension, smoking, and diabetes. This observation lends credence to the premise that parenchymal renal injury and fibrogenesis related to renal atherosclerotic disease develops as a result of multiple layers of microvascular injury. Renal biopsies obtained at the time of renal revascularization commonly demonstrate arteriolar nephrosclerosis and atheroembolic disease, in addition to interstitial fibrosis and glomerular collapse (28).

What are the pathways by which renal interstitial fibrosis develops beyond a vascular lesion? Recent studies in a swine model of atherosclerosis shed some light on this process (22). A schematic summary of the putative interactions between both underperfusion and “ischemic” pathways is illustrated in Figure 2. In the porcine model, microvascular changes in renal endothelial function develop in response to cholesterol feeding alone, a model of atherosclerosis. These are manifest as aber-

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Figure 2. Schematic diagram identifying proposed pathways by which sustained underperfusion of the kidney and/or recurrent episodes of acute ischemic injury might lead to interstitial fibrosis (ischemic nephropathy). These pathways emphasize the interaction between microvascular injury and neurohormonal pathways (renin-angiotensin system and vasoactive prostaglandins). These, in turn, may increase oxidative stress injury and multiple inflammatory cytokines that modulate fibrogenesis in the interstitium. Some of these have been demonstrated, but the interaction and regulation of these mechanisms remain poorly understood. Adapted from reference 64, with permission.
rant responses to vasoactive materials, impaired nitric oxide synthesis, and increased production of isoprostanes, considered a marker for oxidative stress (29). Studies using intravascular ultrasound and endothelium-dependent vasodilators suggest that human kidneys also have disturbances in vascular function and flow reserve (30).

RAS in the porcine model is produced by placement of an irritating copper stent in the renal artery, which stimulates progressive hyperplasia and lumen obstruction. Hypertension develops with transient systemic activation of the renin-angiotensin system, followed by a transition to pressor mechanisms that are dependent on oxidative stress (22). When cholesterol feeding is combined with RAS, further magnification of oxidative stress pathways develops. Tissue fibrogenic cytokines are stimulated in the kidney, reflected by increased TGF-β, NF-κB pathways, and others (31) (Figure 3). Taken together, these studies indicate that multiple pathways, some of which depend on activation of the renin-angiotensin system, participate in renal parenchymal scarring.

Experimental studies demonstrate that repetitive acute insults to the rat kidney can produce acute tubular injury capable of recovery after each episode. However, these repeated insults are capable of provoking fibrogenic mechanisms that produce tubulointerstitial fibrosis much later, which is no longer reversible (32). Such studies raise the possibility that transient episodes of pressure reduction to the poststenotic kidney may induce long-term, cumulative activation of profibrotic mechanisms. Other mechanisms involving oxidative pathways and impaired “clearing” mechanisms for collagen can be demonstrated (31). Maneuvers that use antioxidants to relieve oxidative stress may reduce parenchymal renal injury (33). These studies underscore the complex interaction of vasoactive and fibrogenic factors in the kidney and the limits of our current understanding.

Determinants of the time course for progressive renal injury in ischemic nephropathy are poorly understood. In principle, the more severe and prolonged the vascular injury, the less likely the kidney is to recover after restoring the large-vessel

**Figure 3.** Histologic studies of interstitial fibrosis (Trichrome stain, left two (a) low magnification and high magnification (b) and immunohistochemistry for NF-kappa-B (NFkB, right) in swine. The presence of renal artery stenosis (RAS) induces both interstitial fibrosis and NFkB), which is accelerated by the presence of high cholesterol levels (HC). Data from reference 31, with permission.
blood supply. In most cases, atherosclerotic RAS develops in a setting of preexisting vascular changes affecting the kidney as a result of aging, hypertension, diabetes, dyslipidemia, and occasionally atheroemboli. The mean patient age in published series of renal revascularization has risen from the mid-50s to above 71 yr over the past two decades (34). The level of preintervention GFR tends to predict the likely recovery potential after revascularization, as those with serum creatinine >3.0 mg/dl less commonly improve (35,36). Clinical observations confirm that the rate of loss of GFR just before renal revascularization correlates with the potential for recovery of renal function in the year after endovascular stent placement (37). Studies of diastolic blood flow, such as the Doppler ultrasound renal resistive index, demonstrate that high parenchymal resistance (>80) predicts poor renal functional recovery after successful revascularization (38). Disturbances of papaverine-induced flow reserve in the poststenotic kidney reverse promptly after angioplasty (39). Despite these caveats, individual case reports indicate that even advanced renal dysfunction sometimes can be reversed, particularly when capsular blood vessels are preserved.

Dilemma of Medical Therapy of Renovascular Hypertension and Ischemic Nephropathy: Disease Progression

Candidates who are at risk for ischemic nephropathy usually need extensive medical therapy for other manifestations of atherosclerotic disease. Many of the interventions used to reduce mortality related to stroke and coronary disease undoubtedly extend to atherosclerosis affecting the kidneys. Nonetheless, some authors suggest that the rising incidence of identified RAS may, in fact, be due to the reduced mortality from atherosclerosis in other vascular beds allowing progression of renal artery lesions to reach critical severity (15).

The impact of changing medical therapy for hypertension and other cardiovascular diseases may be greater than generally realized for patients with renovascular disease. In the era before availability of angiotensin-converting enzyme (ACE) inhibitors, <50% of patients with renovascular hypertension could achieve satisfactory BP control. Hence, the search for treatable renal artery lesions often was triggered by severe hypertension. After the introduction of ACE inhibitors, several papers reported successful BP control in 82 to 96% of patients with renovascular hypertension (40). Experimental studies establish that initiation of 2-kidney-1-clip hypertension in the rat can be delayed indefinitely by administration of an ACE inhibitor, confirming the central role of angiotensin II in the early phases of this disorder. As a result, many patients who are treated with agents that block the renin-angiotensin system with early renovascular lesions likely are never identified but simply are treated. Patients who ultimately fail medical therapy represent an important subgroup that warrants close attention and consideration for revascularization. Widespread application of ACE inhibitors/angiotensin II receptor blockers (ARB) and other effective antihypertensive agents partly may be responsible for the rising ages of patients who are sent for revascularization because detection of their disease may have been delayed for years.

Studies of patients with coronary disease and congestive cardiac failure firmly establish the benefits of angiotensin II blockade and/or inhibition for reducing mortality. As noted above, these are among the patient groups most likely to have associated renal artery disease. Although it is widely recognized that patients with bilateral renal artery disease are at risk for functional renal insufficiency during ACE inhibitor and/or ARB therapy, these cases are uncommon in the large trials. Withholding therapy because of a rise in creatinine occurs in 2 to 6% of such patients (41). Whether ACE inhibition itself slows the progression of renal artery disease is not known, although cardiovascular mortality in patients with renovascular disease is reduced in those who are treated with ACE inhibitors as compared with those who are treated without them (42). For all of these reasons, patients with atherosclerotic RAS merit treatment with agents that block the renin-angiotensin system. In view of the cardiovascular benefits of ACE/ARB therapy, developing functional acute renal failure during therapy warrants careful exclusion of renovascular disease. Should it be present, many clinicians consider restoring the ability to use these agents as an appropriate indication for renal intervention.

Atherosclerosis is a progressive disorder. The rate of progression of renal artery lesions depends in part on levels of systolic BP and the magnitude of other risk factors (43). Prospective cohort studies in the 1990s indicated that the most severe lesions may progress to measurably higher arterial velocities in 51% of cases over 3 to 5 yr (43). It should be emphasized, however, that measurable changes in arterial velocities by Doppler ultrasound may not translate into clinical decrements of either renal size or function. Studies from the same group indicate that atrophy (defined as a loss of renal length by 1 cm) develops only in 15 to 20% of the most severe lesions during sequential studies (44). Changes in GFR as reflected by serum creatinine are even less common. These observations confirm clinical experience with “incidental” RAS managed without revascularization. Despite angiographic narrowing of >70% of vessel lumen, clinical progression to refractory hypertension and/or decrements in renal function for which revascularization was recommended developed in only 6 to 10% of 168 subjects (45). A similar study from Europe in patients with incidental RAS identified during peripheral arteriography confirms a minor reduction of estimated GFR in patients with RAS during 8 to 9 yr of follow-up but none who progressed to ESRD (46). Effective therapy with statins may further retard and occasionally regress atherosclerotic renal artery lesions (47). A prospective, randomized study in proteinuric, nondiabetic glomerular disease indicates that statin therapy reduces proteinuria beyond the levels achieved with ACE inhibition alone (48). Taken together, these observations suggest changing rates of progression for both atherosclerosis and kidney disease, in part related to vigorous intervention with ACE inhibition, statins, and BP reduction. How effective these maneuvers will be in the general population is not yet known.
When to Pursue Renal Revascularization for Ischemic Nephropathy

A detailed examination of the effects of surgical, angioplasty, and endovascular stent series is beyond the scope of this review. Many of the renal functional outcomes of these series are summarized elsewhere (49,50). It should be emphasized that recent small, prospective trials of renal angioplasty (mostly without stents) in selected patients produced only modest improvements in BP (51–53). These results have led some authors to favor medical management primarily for renovascular hypertension (54), although it must be recognized that these trials had crossovers to renal revascularization (in one series, 44% of medically assigned patients) because of refractory hypertension. From a practical point of view, factors that favor renal revascularization include failure to achieve excellent BP control, episodes of congestive heart failure, or progressive renal insufficiency, as we have argued (55). Developments in endovascular stent technology continue to improve and can restore vessel patency. Improved techniques seem to reduce restenosis and acute procedural complications.

Perhaps the most striking feature of these studies, however, has been the ambiguity of the composite clinical results after interventional procedures to kidneys with renal dysfunction, as we have emphasized previously (56). In most series, the group values of GFR are minimally changed during long-term follow-up. As shown in Figure 4, average values do not accurately represent the actual outcomes of individual patients. Some (27%) patients recover renal function in a dramatic manner and for durable benefit (Figure 4, left) (56). Few would disagree with the contention that improvement in GFR reflected by a fall of serum creatinine of 4.5 to 2.2 mg/dl is a major benefit and obviates the imminent need for renal replacement therapy in many cases, as has been again emphasized (6). A recent series of 261 patients who underwent renal artery stenting also demonstrated reduced mortality from cardiovascular events in subsequent years in the subgroup whose final estimated GFR was >40 ml/min (19). The benefits of revascularization for such a subgroup are reflected in other recent series, particularly those with RAS affecting the entire renal mass (57). Most patients who were subjected to intervention have little or no change in kidney function (Figure 4, middle) but may be at lower risk for progressive vascular occlusion in the future (although they remain at risk for restenosis and/or other complications). What is most troublesome about vascular intervention in atherosclerotic disease is the inevitable subset of patients who develop worsening renal function soon after revascularization procedures (Figure 4, right). This is observed in patients who underwent surgery, angioplasty, or stenting (58,59). In some series, this proportion comprises 19 to 25% of patients, whose deterioration in renal function can be abrupt and progressive. Outcomes in this group are dramatically worse than outcomes in the group whose renal function improves. Some series report >35% progression to require dialytic support and accelerated mortality (60).

The precise cause of deteriorating kidney function after renal revascularization remains poorly understood. Undoubtedly, atheroemboli related to disrupted wall plaque play an important role. Studies in renal and other atherosclerotic vessels using distal devices to catch debris downstream from intervention suggest that atheroembolic showers are nearly universal after instrumentation (61). An example of the delayed but inexorable clinical deterioration encountered in such a patient is illustrated in Figure 5. Whether angiographic distal protection devices ultimately will protect the kidney and obviate this...
process remains to be seen. Whether other processes related to restoring renal blood flow also aggravate tissue injury is an important question. Experimental studies in other vascular beds indicate that reperfusion injury can develop under some conditions, particularly when toxic oxidative species are favored (62). At some point, activated cytokines may produce parenchymal scarring that is no longer dependent on large-vessel injury and will progress regardless of vessel repair. Whether some of the fibrogenic pathways in the kidney can be modified independent of vascular intervention is an important area of research.

**Frontiers in Ischemic Nephropathy: What We Need to Define Further**

At this point, there is no doubt that some patients develop meaningful loss of renal function beyond large-vessel occlusive disease. It is equally clear that many patients with atherosclerotic RAS have “incidental” disease with little hemodynamic impact. Major gaps in our understanding of this disorder merit close study. Several of these are listed in Table 1. A major focus of cardiovascular research until now has been on the nature of atherosclerotic disease processes and the effects of vascular repair, with either endovascular or surgical techniques. Although a rich literature addresses functional predictors of BP responses, meaningful predictors of renal function after revascularization are sparse. These areas invite further investigation and will offer major contributions both in the pathophysiology of tissue injury and in clinical outcomes.

Whether better understanding of the precipitating signals and fibrogenic pathways will produce the means to improve patient selection and/or to protect the kidney without vascular intervention is not known. A major goal of clinical studies must be to apply endovascular procedures toward patients who are most likely to benefit and/or least likely to have adverse outcomes as noted above.

The widespread character and enormous comorbidity of atherosclerosis makes clinical decision making in this disorder complex. Up to now, small, prospective studies have failed to establish survival advantage attributable to renal revascularization (45,63). A recently proposed study (CORAL) has the goal of examining whether randomization of patients to endovascular stent therapy reduces combined cardiovascular events, mortality, and renal end points when added to carefully standardized medical therapy of patients with proven renovascular disease (Christopher Cooper, Medical College of Ohio, Toledo, June 2004). The study proposes randomizing >1000 subjects to attain sufficient power to answer its main questions. That such a study is tenable and needed illustrates the state of “equipoise” and uncertainty surrounding the decision regarding stent therapy for atherosclerotic RAS. Even after the results of such a study are available, clinicians likely will find defining the risks and benefit analysis of intervention in atherosclerotic renovascular disease challenging for individual patients. This disorder is best identified early and followed carefully. Experience has shown that many lesions remain stable for years and pose little clinical hazard. Success in managing ischemic nephropathy will continue to depend on vigilant clinicians to

**Table 1. Partial list of major areas of research needed in ischemic nephropathy**

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<th>Vascular disease</th>
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<td>mechanisms of lesion development, progression, and hemodynamic effects in early disease</td>
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<td>interaction with preexisting microvascular disease</td>
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<td>hormonal and neurohormonal mechanisms regulating vascular control and regional blood flow distribution in an underperfused kidney</td>
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<th>Signaling mechanisms inducing parenchymal renal injury</th>
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<td>role of signaling molecules/neurohormonal pathways during loss of pressure interaction and “cross-talk” between signaling pathways means of modulating signaling pathways</td>
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<th>Elucidation of fibrogenic pathways</th>
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<td>role of fibrogenic cytokines: TGF-β, NF-κ, etc. role of oxidative injury/stress modulation of fibrogenesis</td>
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<th>Clinical identification and intervention</th>
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<td>functional studies to define “critical perfusion” threshold optimal methods to track progression of identified vascular lesions diagnostic markers to identify real-time fibrogenic processes, both to identify initiation and stage of renal injury and to tracking intervention study of medical intervention to modify fibrogenic pathways, oxidative stress, and cytokine pathways study of the effects of vascular reperfusion to identify timing and optimization of endovascular repair</td>
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identify progressive lesions and to intervene on critical stenoses before renal parenchymal injury becomes irreversible.

References


Ischemic Nephropathy 1981


Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/