Atherosclerotic Renal Artery Stenosis: Overtreated but Underrated?

Stephen C. Textor
Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota

ABSTRACT
Despite evidence of only moderate clinical benefit, application of renal endovascular stent procedures has increased at least four-fold in the past decade. Medicare is reviewing national coverage regarding reimbursement, questioning whether outcome data warrant many of these procedures. Several prospective, randomized trials are now in progress to compare outcomes with optimized medical therapy with and without stenting. Current imaging methods establish primarily the presence and severity of vascular occlusive disease. Optimal treatment for individual patients remains in flux and is reviewed here. Most important, nephrologists await development of tools to predict reliably when renal parenchymal injury is beyond recovery and/or when revascularization can produce meaningful salvage of kidney function.


A remarkable drama unfolded in 2007 regarding renovascular disease. The Center for Medicaid and Medicare Services (CMS) convened a meeting of its medical advisory group regarding treatment of renovascular disease, specifically atherosclerotic renal artery stenosis (RAS). The introductory statement read as follows: “In view of the uncertainty regarding optimal strategies for evaluation and management of atherosclerotic RAS, as well as the controversy about the risks and benefits of treatment, the CMS internally generated in February 2007 a national coverage analysis to examine the best treatment of RAS.”

That CMS is reviewing its payment coverage for atherosclerotic RAS undoubtedly reflects the increase in endovascular stenting procedures for Medicare beneficiaries, rising from 7660 in 1996 to 18,520 in 2000.1 Estimates at the meeting suggested this increased further to more than 35,000 in 2005. The largest portion of this increase derives from procedures undertaken by cardiologists.1 Recent guidelines from professional organizations based on admittedly weak data lend support to the application of interventional vascular procedures into the renal arteries and inclusion of renal arteriography as part of coronary angiographic procedures.2,3 As part of their review, CMS commissioned an analysis of published information regarding the benefits of revascularizing the kidney for atherosclerotic RAS by the Agency for Healthcare Research and Quality. The results of this analysis were published in December 2006. The authors of this review concluded that available information was insufficient to support benefits regarding mortality, progressive kidney disease, or cardiovascular events.4 Thus, the published literature cannot support the observed, massive expansion of endovascular intervention.

During the same time interval, at least four prospective, randomized trials for atherosclerotic RAS were started to examine the role of medical therapy alone as compared with medical therapy plus stent revascularization. In the United States, the National Heart, Lung, and Blood Institute of the National Institutes of Health is funding the Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL) trial. This trial seeks to randomly assign 1080 patients to “optimal medical therapy” with or without renal artery stenting and evaluate clinical events including death, stroke, coronary artery disease events, congestive heart failure, kidney failure, and uncontrolled hypertension.5 A central premise of CORAL is that neurohormonal activation (mainly of the renin-angiotensin and sympathoadrenergic system) largely determines the morbidity from RAS. This trial has had difficulty meeting enrollment goals despite the increasing application of stent procedures. That the National Institutes of Health and more than 70 institutional review boards accept that management of atherosclerotic RAS is currently in “equipoise” regarding the added value of renal revascularization again challenges the expanding use of interventional therapy. How CMS will ultimately cover reimbursement for renal artery stenting has yet to be settled.

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surgery has been mostly replaced by endovascular stent therapy for atherosclerotic
disease. The introduction of intensive medical therapy including ACE/ARB and calcium
channel blockers, plus statins, aspirin, and diabetes management, has allowed effective
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spective trials have failed to identify major benefits of revascularization as compared with
medical therapy (see text). Larger, prospective trials are enrolling higher risk patients who
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mental respects from vascular occlusive
disease affecting the heart, brain, or ex-
tremities. The interactions between vas-
cular disease and kidney function, arte-
rial pressure, and volume control are
complex. Clinical syndromes associated
with RAS now arise more frequently than
ever for patients who have other vascular
disease involving the coronary and pe-
ipheral vascular beds. Some estimate
that up to 5% of patients who reach
ESRD may have renal artery stenosis as their primary kidney disorder. This lin-
gering concern means that for any single
patient with worsening hypertension and declining kidney function, neph-
rologists are forced to consider the po-
tential role of large-vessel atherosclerotic
disease. Although many patients can be
treated effectively and safely with current
medical therapy, selection of individuals
who will benefit from renal revascular-
ization and for whom its risks are war-
ranted poses a major clinical challenge.

In some respects, these developments
reflect stunning successes of basic and
clinical research. Diagnostic imaging and
therapeutic options have advanced rap-
idly in the past two decades. Major mile-
stones in the evolution of our under-
standing of renovascular hypertension and ischemic nephropathy are summa-
rized in Figure 1. Early observations that
placement of a renal artery clip produces
a rise in systemic arterial pressure was
among the first evidence firmly linking the
kidney to cardiovascular control. For
many years, patients with severe hy-
pertension were examined for the pres-
ence of renovascular hypertension with
the goal of either removing the offending
kidney or revascularizing the kidney us-
ing surgical techniques. Available antihy-
pertensive drug therapy (mainly sympa-
tholytic agents such as methyldopa,
reserpine, or guanethidine) often fail to
control dangerous, sometimes “malign-
ant phase” hypertension in such indi-
viduals. In extreme cases, patients under-
went bilateral nephrectomy as a life-
saving measure to prevent episodes of
recurrent hypertensive encephalopathy
or pulmonary edema. These reports co-
incide with the introduction of renal re-
placement therapy with dialysis.

Studies of the mechanisms by which a
renal artery clip produces hypertension
paved the way to define the renin–angio-
tensin–aldosterone system (RAAS) and
were fundamental to development of pharmacologic tools to block this system.
The first agents available (Sar-1-Ala-8-
angiotensin, or saralasin) to block the
angiotensin receptor were targeted pri-
marily at renovascular hypertension.
Since then, many studies have identified
complex interactions between angioten-
sin and kidney function, vascular remod-
eling, recruitment of additional pressor
mechanisms, and neurohormonal acti-
vation. Studies of genetic knockout
models free of the angiotensin receptor
(AT1a knockout) extend these observa-
tions to demonstrate critical roles for
both kidney and systemic receptor activ-
ation for angiotensin II–dependent hy-
pertension. The development of oral
agents that interrupt the RAAS provided
for the first time well-tolerated drugs
that improved BP control and reduced
cardiovascular risk for patients with ren-
ovascular hypertension. Wider applica-
tion of renin-angiotensin system block-
ade now provides hope that many forms
of progressive kidney injury, congestive
heart failure, and vascular disease may be
relieved to a degree never imagined by
those first studying renovascular hyper-
tension.

RAAS blockade, statins, and anti-
platelet therapy are now bedrocks for the
clinical management of atherosclerotic
disease, including RAS. Although the
benefits of restoring blood flow to the
kidney may seem to be obvious, vascular
stenting carries well-recognized risks of
atheroembolic disease, restenosis, and
local complications, such as vessel dis-
section and thrombosis, that remain
problematic; therefore, whether endo-

Figure 1. Milestones in identification and treatment of renovascular hypertension and ischemic nephropathy: Renal revascularization was possible first in the 1960s and was the only effective antihypertensive therapy for severe renovascular disease. The introduction of agents that block the renin-angiotensin system (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARB]) changed the landscape dramatically. Surgery has been mostly replaced by endovascular stent therapy for atherosclerotic
disease. The introduction of intensive medical therapy including ACE/ARB and calcium
channel blockers, plus statins, aspirin, and diabetes management, has allowed effective
therapy for many patients considered untreatable before. Recent small, short-term, pro-
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vascular stenting provides additional benefit beyond meticulous management of BP, blockade of neurohormonal activation, and management of other risk factors is controversial. This is the basic question underlying current prospective treatment trials such as CORAL and ASTRAL (Angioplasty and STent for Renal Artery Lesions). Nephrologists have moved toward a more conservative clinical stance in recent years, perhaps as a pragmatic counterweight to enthusiastic interventional cardiologists and radiologists. The challenge facing thoughtful clinicians in this arena is to prevent such conservatism from interfering with the best interests of patients who could benefit from renal artery revascularization to a major degree.

Among the problematic features of atherosclerotic RAS has been the poorly defined relationship between the presence of large-vessel occlusive disease and target injury in the kidney. Unlike fibromuscular disease, the degree of severity of vascular occlusion in atherosclerosis bears little relationship to measured blood flow, kidney volume, degree of fibrosis, or GFR. These observations provide the basis for experimental studies of interactions between vascular occlusion and other vectors of kidney injury, including endothelial dysfunction, tissue oxidative stress, and the atherosclerotic milieu produced by dyslipidemia (Table 1). It is unclear whether high-grade vascular occlusion induces repeated episodes of transient kidney ischemia that activate profibrotic pathways similar to other acute models. How to identify regional “ischemia” in living animals is not yet certain. Recent studies using blood oxygen level dependent magnetic resonance indicate that poststenotic kidneys have a range of metabolic activity and oxygen consumption linked to active solute transport. Our initial studies suggest that total vascular occlusion and loss of filtration is associated with reduced levels of deoxyhemoglobin and minimal change during furosemide administration. By contrast, viable, functioning kidneys beyond an atherosclerotic lesion have relatively high levels of accumulated deoxyhemoglobin, particularly in the medulla. Such kidneys can respond briskly to reduce deoxyhemoglobin levels after intravenous administration of furosemide to reduce solute transport. Whether elevations of deoxyhemoglobin and furosemide-suppressible oxygen consumption induce cytokine release or toxic oxidative stress is an important question that warrants further study.

It is almost certain that many, if not most, patients now being subjected to endovascular stenting of the renal arteries have only limited benefit, regarding either BP response or improvement in kidney function. Equally important to recognize is that a subset of patients with “critical” renal artery stenosis stand to have major clinical benefit from restoring kidney perfusion and major adverse outcomes if not detected and treated. Summarized in Table 2 are a series of clinical issues that address whether patients are likely to warrant renal revascularization. Most imaging procedures focus on the first two items—the anatomic severity and approachability of renal vascular lesions. It is likely that the third and fourth items—diagnostic measures to evaluate the role of vascular occlusive lesions in generating disease and the likelihood of clinical benefit after restoration of vessel patency—are more important. Further studies in the renal vasculature should be aimed at defining these char-

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**Table 1. Interactive mechanisms underlying hypertension and kidney injury in atherosclerotic RAS**

<table>
<thead>
<tr>
<th>Tissue Underperfusion</th>
<th>Recurrent Local Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation of renin-angiotensin system</td>
<td>ATP depletion</td>
</tr>
<tr>
<td>Altered endothelial function (endothelin, NO, prostaglandin)</td>
<td>Tubulointerstitial injury</td>
</tr>
<tr>
<td>Sympathoadrenergic activation</td>
<td>Microvascular damage</td>
</tr>
<tr>
<td>Increased reactive oxygen species</td>
<td>Immune activation</td>
</tr>
<tr>
<td>Cytokine release/inflammation (NF-κB, TNF, TGF-β, PAI-1, IL-1)</td>
<td>Vascular remodeling</td>
</tr>
<tr>
<td>Impaired tubular transport functions</td>
<td>Interstitial fibrosis</td>
</tr>
<tr>
<td>Apoptosis/necrosis</td>
<td>RAAS</td>
</tr>
<tr>
<td></td>
<td>Sympathoadrenergic activation</td>
</tr>
<tr>
<td></td>
<td>Endothelin</td>
</tr>
<tr>
<td></td>
<td>Disturbances of “oxidative stress”</td>
</tr>
<tr>
<td></td>
<td>Oxidized LDL</td>
</tr>
</tbody>
</table>

*NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1.

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**Table 2. Issues central to determining role for renal revascularization in atherosclerotic RAS**

<table>
<thead>
<tr>
<th>Questions</th>
<th>Tools for Evaluation</th>
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<tbody>
<tr>
<td>Severity of vascular occlusion?</td>
<td>Quantitative angiography, translesional gradients, intravascular ultrasound</td>
</tr>
<tr>
<td>Treatable?</td>
<td>Vessel location, associated disease, accessory vessels, aneurysm, occlusion</td>
</tr>
<tr>
<td>Responsible for disease?</td>
<td>Evident activation of pressor systems (e.g., renin)</td>
</tr>
<tr>
<td></td>
<td>Duration of change (e.g., BP) renal function; other measures of tissue ischemia (e.g., BOLD MR, PET energy consumption); activation of fibrogenic, inflammatory, or oxidative pathways</td>
</tr>
<tr>
<td>Benefit from revascularization?</td>
<td>Rapidity of evolution, preexisting injury (e.g., hypertension, diabetes, other kidney disease), comorbid disease risk, associated procedural risk to kidney (e.g., atheroembolic potential), response to other medical therapy</td>
</tr>
<tr>
<td></td>
<td>Risk for disease progression, salvageability of kidney function (resistive index, BOLD MR)</td>
</tr>
</tbody>
</table>

*BOLD MR, blood oxygen level dependent magnetic resonance; PET, positron emission tomography.*
characteristics more fully. A recognized drawback of clinical treatment trials, of course, is the intermixture of high-risk and low-risk patients into the “average” of the entire cohort. Although prospective, randomized trials are essential, clinicians remain in sore need of better tools to identify renal parenchyma at true risk for “ischemic injury” and to identify when kidney function can be (or can no longer be) improved with renal revascularization.

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DISCLOSURES

None.

REFERENCES


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