Part One: The Vast Majority of Patients with Renal Artery Stenoses Require Intervention

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Introduction

The debate position given to this author may on first glance appear to be untenable. I hope to convince you that the opposite stance of not treating patients with renal artery stenosis (RAS) neglects the opportunity to help some patients with correctable hypertension and renal dysfunction. Frankly, either debate position is difficult to defend given our dearth of solid information in the arena of renovascular disease. As a medical community, we have scant evidence on the natural history of renal artery stenosis and the kidneys these arteries are supplying. Furthermore, the available data is far from convincing especially given the flawed trial designs in most of the prospective trials. Clearly, further study on renovascular disease may lead us to better medical management, patient selection for intervention, and technical success in those patients that are intervened upon. I do not believe a global position of benign neglect of renal artery disease will be in the best interest of patients with this morbid condition. There are some current posits that require re-examination. The following widely held myths need scrutiny:

Myth 1. Atherosclerosis in the renal arteries is benign

In every arterial bed, the severe consequences of arterial narrowing secondary to atherosclerosis are recognized. The
within 2 years. Similarly, using ultrasound to document disease per year with 11% progressing to renal occlusion or thrombosis is well recognized as life-saving by both medical professionals and laypersons. Why should the kidneys be different? The natural history of RAS is variable. But, a significant fraction of patients with RAS have progressive narrowing of the inflow artery to the functioning renal mass. Using Doppler follow-up, Zierler and colleagues showed renal arteries with significant stenoses (>60%) have approximately a 20% progression of disease per year with 11% progressing to renal occlusion within 2 years. Similarly, using ultrasound to document renal size, Caps and colleagues showed progression to renal atrophy in patients with worsening renal artery stenosis. It is estimated that chronic kidney disease affects 11% of the adult population in the United States with nearly 400,000 patients with end-stage renal failure. The morbidity and mortality of end-stage renal disease is staggering with U.S. annual mortality rates of greater than 20%. Even lesser degrees of chronic kidney disease can have significant consequences as the risk of death increases as the glomerular filtration rate (GFR) falls. Furthermore, reduced GFR is independently associated with the cardiovascular morbidity and hospitalization with severe renal impairment (GFR < 30 ml/min/1.73 m²). Despite the prevalence of chronic kidney disease, the relationship to RAS remains unclear. A significant fraction of patients on hemodialysis have renal vascular disease implicating that RAS may be an underappreciated component of renal failure.

Myth 2. Patients with hypertension and renal artery stenosis have renovascular hypertension

One of the critical problems in assessing patients with renal artery stenosis is the unclear relationship with concomitant hypertension. Goldblatt’s compelling studies helped the medical community understand the causal relationship of RAS to hypertension over 70 years ago. This led to several reports of curing hypertension by surgical revascularization a few years later. In pediatric or young adult populations with congenital or vasculitic causes of renal artery stenosis, hypertension is closely aligned to the degree of unilateral RAS. With increasing unilateral stenosis, neurohormonal changes occur resulting in increased angiotensin II induced blood pressure elevation. In older populations, essential (or primary) hypertension is rampant and appraising whether the RAS is a bystander or the culprit can be challenging for even the most experienced practitioner. A cavalier attitude by some is that in our current limitations of understanding this relationship, the only way to tell is the response after intervention. That is, treat everyone, help a few. Clearly, this position of “drive-by” stenting can lead to inappropriate use of technology, increased costs, and the real possibility of patient harm in cases of inadvertent renal injury.

Patients with severe hypertension with episodes of hypertensive crises appear to be the best candidates for RAS intervention. The severity of hypertension may be seen as the need for increasing antihypertensive agents, increased dosage or frequency of medication, and sudden worsening in blood pressure control in an otherwise stable patient. Despite a plethora of studies to try to understand this relationship of RAS and hypertension, most studies (i.e. renal vein renin sampling), are not sufficiently sensitive or specific to clearly implicate the RAS as the etiologic factor for the hypertension. A test with prognostic value in this arena will allow careful selection of patients that require intervention. Lastly, the current data on blood pressure reduction in trials is grossly estimated by the number of medications and/or reduction in dose as a surrogate to actual blood pressure measurements. The latter is a widely fluctuating physiological parameter and deserves a more precise assessment.

Myth 3. Ischemic nephropathy is any patient with an escalating creatinine and bilateral RAS

As opposed to unilateral RAS and resultant renovascular hypertension, bilateral RAS or stenosis in the artery leading to a single functioning kidney may lead to renal function loss. Renovascular hypertension may be overdiagnosed, but RAS causing renal insufficiency and eventual renal loss may be underdiagnosed and consequently undertreated. This condition called “ischemic nephropathy” can be treated and leads to gratifying improvement in renal function. However, the tools to assess this in our current practice are the poorly sensitive serum creatinine (sCr), the GFR with calculations often based on sCr, and nuclear medicine testing where the images and interpretation can sometimes be challenging and lead to differences in subjective impression between observers. Unfortunately, most patients with “ischemic nephropathy” presumably have renal function decline secondary to unrelated chronic renal disease from intrinsic renal glomerular loss secondary to a host of systemic processes. This may include inflammatory conditions and oxidative stress.

Similar to Myth #2, the likelihood of understanding in a particular patient whether renal function decline is due to RAS is often difficult. Many experienced practitioners have had the gratifying situation of observing rapid improvement in renal function after treating severe RAS to a single functioning kidney where the serum markers clearly delineate residual renal function. Likewise, the experience of patients with no improvement in their renal function despite a technically successful procedure is not uncommon. Salvage of the kidneys is best predicted by the downward slope of GFR or renal function prior to intervention. Other prognostic modalities to identify renal...
mass retrieval may be novel MR based methods to understand the perfusion deficit in patients with ischemic nephropathy. Novel technologies and assays would allow us to determine an infarcted renal mass from one that is ischemic, analogous to stress testing and biomarkers in the coronary beds.

Myth 4. Renal stenting is an easy procedure to do well

For the purposes of this debate, we are assuming intervention of the renal arteries means endovascular intervention. There is rich literature on the benefits of surgical revascularization of the renal arteries. Surgical revascularization for retrieval of renal function can be accomplished with documented durable long-term results in centers of excellence with a dedicated interest in renal vascular surgery. However, this has largely been supplanted by endovascular means because of the perceived lower initial morbidity of a purely percutaneous procedure as opposed to open revascularization in an elderly population with multiple co-morbidities.

Technical advances have also spurred widespread adoption of endovascular treatment of RAS. Despite the rapid increase in renal stenting, trial data have documented the harm that can occur to the kidneys that we are trying to protect from deterioration. The kidney does not have the same discrete functional areas that would alert a clinician to kidney decline after intervention other than where serious harm has occurred because of large emboli, renal infarction, dissection, reperfusion injury, or contrast-induced renal failure. Some of these may happen more than we realize. Some possible technical adjuncts that prevent these complications include: adopting a 6 Fr platform for intervention with the use of 0.014” guidewires and stent systems, rapid exchange systems, using a distal protection device, using a “no touch” technique, anticoagulation/direct thrombin inhibition, and routine peri-procedure double anti-platelet therapy with aspirin and clopidogrel. Clearly in other arterial beds, a distal protection device can be used to capture atheroembolic debris prior to reaching a distal protection device during renal intervention makes intuitive sense given the capture of embolic debris in a significant fraction of cases.

Additional evidence that atheroembolic material can cause renal parenchymal damage has been obtained via an ex vivo study using human arterial plaque specimens. Currently, the outcome of renal PTA/S with a distal protection device is being evaluated in the NIH-supported randomized controlled Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial.

Myth 5. The data from randomized trials are clear-cut

My debate opponent will try to convince you that multiple randomized controlled trials clearly show no benefit from renal artery stenting. One thing is clear: no benefit can be obtained in patients poorly selected for intervention. Another critical point: Any benefit from an intervention can be negated by the poor performance of the procedure.

In the recent STAR publication, the investigators randomized 140 patients to medical therapy or renal artery stenting for atherosclerotic disease in the renal arteries at 10 European medical centers. Patients were eligible for inclusion if creatinine clearance was <80 mL/min per 1.73 m² and they had a 50% or greater stenosis. The primary endpoint was a 20% or greater fall in creatinine clearance. This occurred in 16% of the stent group and 22% of the medication group (P = NS). The authors concluded that stent placement had no clear benefit on preventing renal function decline in this small study. Of note, only 46 or the 64 patients assigned to stenting actually had a stent placed. Of great concern was that 12 of the 64 patients (19%) did not get a stent because they had <50% stenosis at time of angiography despite the preoperative imaging (CTA, MRA, etc.) indicating a high-grade stenosis. One can assume that the medical therapy group also had a large fraction of patients with insignificant and benign renal artery stenosis (<50%). The rates of complications in the stented group including 2 procedure-related deaths, 1 death from an infected hematoma, 1 renal failure after kidney cholesterol embolism, 2 technical failures, and 10 femoral hematomas paint a troubling picture in a group of 46 renal stent procedures.

ASTRAL is an international, multicenter trial that enrolled 806 patients and randomized them to intervention or medical management. The primary outcome was again renal function measured as a reciprocal of the serum creatinine level. The two groups had similar rates of renal events, cardiovascular events, and death as will be outlined by our debate opponent. But, this trial has many limitations. Of greatest concern were the inclusion criteria of patients into the trial. Patients were eligible for enrollment if they had atherosclerotic disease in the renal arteries and were considered suitable for endovascular revascularization. However, only 59% of enrolled patients had a renal artery stenosis greater than 70% with essentially the remainder having 50–70% stenoses. Physicians did not enroll patients if they thought that renal revascularization would be beneficial—the exact target that any RCT in this arena should focus on. Thus, the patients that we assume would have the greatest benefit from revascularization were excluded. Neither the medical management nor the intervention techniques were standardized and there was no core laboratory to review the images and corroborate the renal artery stenoses treated. In fact, often the severity of the stenosis is overestimated by the interventionist when compared to the core laboratory’s non-biased assessment. Thus, many of these patients may have actually had modest (i.e. 50%) stenoses, rather than critical stenoses to the kidney they were trying to protect. Seventeen percent of patients did not undergo intervention after angiography because the severity of renal artery stenosis by noninvasive methods was not confirmed on angiography—one can assume a similar proportion of low-profile lesions in the medical group. Additionally, 40% of enrollees had serum creatinine levels <150 umol/L (<1.7 mg/dL) with a large fraction of these patients with normal creatinine and only on an average 2.8 antihypertensive agents. What was the indication for treatment in these patients? In the 359 patients that actually underwent revascularization, 31 patients (9%) had complications. This included renal embolization (5), renal artery occlusion (4),
renal artery perforation (4), femoral artery aneurysm (1), and cholesterol embolization (3) leading to gangrene and amputation. With any revascularization procedure for atherosclerosis, we are trying to "beat" the natural history of the disease. Patients that have high-grade renal artery lesions, rapidly falling GFR, and stenoses to the whole renal mass (i.e. bilateral renal stenoses, stenosis to a single-functioning kidney) may benefit from renal stenting. But, trials that enroll large fractions of the patients with benign lesions and then have high complication rates cannot be expected to be successful.

Conclusions

With the current data available, one may not be able to conclude that "vast majority of patients with renal artery stenoses require intervention", the provocative position assigned to this author. On the other hand, the position "the vast majority of patients with renal artery stenoses do not require intervention" leaves many patients without an option that may be kidney- and life-saving. We all agree that more research is needed in this area. One day, clinicians will be able to discern that a particular renal artery stenosis is the culprit that leads the kidney end-organ to cause hypertension and/or become ischemic and atrophy. In the interval, careful evaluation of patients with renal artery stenosis and renal insufficiency by a collaborative team of nephrologists and vascular specialists appears to be warranted. This may offer patients the best opportunity for long-term renal salvage and survival, whether it be medical treatment or intervention.

References


Part Two: The Vast Majority of Patients with Atherosclerotic Renal Artery Stenoses do not Require Intervention

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Introduction

The rate of percutaneous renal artery intervention among Medicare beneficiaries increased 2.4-fold in 2000 as compared with 1996 on the premise that associated hypertension and renal function would be cured.1 To date, however recent randomized controlled trials (RCT) on primary stenting for atherosclerotic renal artery stenosis (ARAS) are not supporting evidence for its use.2 The goal of this debate was to summarize the evidence on percutaneous renal artery stenting for ARAS.

The Clinical Problem

The reported incidence of atherosclerotic renal artery stenosis (ARAS) in the Medicare population is 0.5% overall,3 but as these patients are often asymptomatic the true frequency of ARAS is probably higher. ARAS is associated with hypertension, chronic kidney disease and cardiac disorders, although it is not clear whether these associations are causal.4 Nevertheless, patients with ARAS after adjustment for other traditional risk factors, are at increased risk for cardiovascular events with a risk of coronary event that is increased by a factor of two and markedly decreased survival.5 These outcomes are rare in patients with ARAS that are treated medically6 and probably related to distribution and severity of atherosclerosis in other vascular beds.7,8

Evaluation

ARAS is suspected in patients with the onset of hypertension after 50 years of age. Confirmation of the diagnosis is made by imaging. Doppler measurement of renal artery velocity provides an assessment of the severity of the stenosis. Alternative methods include MRA, computed tomographic angiography (CTA) and digital subtraction angiography with the use of small catheters and limited amounts of contrast media. All these tests are useful in confirming the diagnosis of ARAS, but Drieghe et al.9 have shown that even if renal angiography and color duplex ultrasound correlate well, both approaches tend to overestimate the ARAS severity when compared with the measured trans-stenotic pressure gradient using 0.014 pressure wires. Again none of these techniques can establish the functional significance of ARAS. Even the documentation of a trans-stenotic pressure gradient in ARAS does not necessarily mean that the given stenosis is the cause of hypertension.

Risk Factors and Medical Treatment

A major confounder related to the treatment of ARAS is competing risk from other manifestations of atherosclerosis including stroke, acute coronary syndrome, and congestive heart failure. The risk of these events is greater than the risk of complications related specifically to ARAS. They reflect widespread atherosclerotic disease elsewhere.10 In this context, medical therapy remains the cornerstone of treatment for ARAS. Multi-drug regimens are needed for blood pressure control including renin-angiotensin-aldosterone inhibitor, alpha or beta-blocker, diuretic and calcium channel antagonist. The demonstrated benefits of antiplatelet therapy and statins in patients with atherosclerotic disease also provide support for their use in patients with ARAS.

Prospective Randomized Controlled Trials

Benefit of renal stenting over angioplasty alone

Primary stenting of ARAS was compared to angioplasty alone in one small RCT.11 The results of this trial were comparable with those of a meta-analysis that compared these two techniques.12 There was a 65% reduction in risk of restenosis with stents at 6-months angiography but there was no difference in blood pressure or renal outcome. Primary stenting thus showed a more favorable outcome with fewer reinterventions than angioplasty for ARAS.13

Benefit of renal artery stenting vs. surgery

Only one RCT compared renal artery stenting vs. open surgical revascularization in patients with ARAS.14 Inclusion criteria were severe hypertension and ARAS >70%. There was no significant difference in treatment outcome i.e., blood pressure, renal outcome, mid-term patency and complications. But as surgery was associated with a longer duration of hospitalization (18 days vs. 10 days), the authors suggest that renal artery stenting should be preferred to surgery in patients who do not need concomitant aortic revascularization.