Is renal artery stenting the correct treatment of renal artery stenosis?

The Case for Renal Artery Stenting for Treatment of Renal Artery Stenosis

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The case favoring renal artery stenting for individuals with renal artery hypertension is largely circumstantial. At best, the clinical evidence presented in this discussion is derived primarily from nonrandomized cohort studies. It would certainly be easier to argue that medical therapy is preferred for such individuals because there are 3 published randomized clinical trials that concluded just that and none that support renal artery intervention. Nonetheless, there is considerable evidence to support the role for revascularization in general, and stenting specifically, as an important adjunctive therapy to medical therapy in the care of patients with renal artery stenosis (RAS). The argument has 3 principal components: observations about the impact on cardiovascular physiology, end-organ effects, and natural history.

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RAS and Hypertension

RAS is associated with and is an important cause of secondary hypertension. RAS causes endocrine activation with release of renin from renal juxtaglomerular cells. Renin catalyzes the breakdown of angiotensinogen to angiotensin I. Angiotensin I is transformed by angiotensin-converting enzyme into angiotensin II, and angiotensin II promotes the release of aldosterone from the adrenal cortex. Angiotensin II is a potent vasoconstrictor, substantially more potent than epinephrine, and is implicated in end-organ damage in the heart and kidney. RAS is suggested to cause 2 types of hypertension. With unilateral RAS and a normally perfused and normally functioning contralateral kidney, blood pressure elevation is referred to as “renin dependent” and is characterized by increased peripheral resistance. In this circumstance, renin and angiotensin levels remain elevated, but volume expansion is limited by natriuresis of the contralateral normally functioning kidney. Importantly, although renin levels are elevated, the value of peripheral or even renal vein renin values is limited by substantial overlap with patients having essential hypertension.

When stenoses are bilateral or when the contralateral kidney is absent or is dysfunctional, intravascular volume increases and renin secretion decreases over a period of 5 to 10 days. Without the natriuretic effect of a normally perfused contralateral kidney, hypertension is maintained by volume expansion. This scenario is described as 1-kidney 1-clip Goldblatt hypertension.

In addition, the sympathetic and central nervous systems contribute to hypertension in RAS. RAS also causes increased production of vasoactive reactive oxygen species, which increases vasomotor tone. Ischemic injury of the affected kidney(s), hypertensive nephrosclerosis of the contralateral kidney, or hypertrophy of the peripheral vasculature also may be important contributors to sustained hypertension.
with RAS. Abnormal endothelium-dependent vasodilation also appears to be found and may be associated with increased oxidative stress. Recent work suggests that primary hyperaldosteronism may contribute to the persistence of hypertension in a significant minority of patients who appear to be unresponsive to revascularization.

Thus, it is clear that hypertension is an important consequence of RAS. Antihypertensive medical therapy may address one or several of these mechanisms, but revascularization with endovascular stenting may be an efficient mechanism to downregulate many of these changes. As an example, successful renal artery revascularization may decrease muscle sympathetic nerve activity, as does denervation of the affected kidney, and may improve endothelial function.

RAS and Kidney Function

Although end-stage renal disease is uncommon in the short term, historical data suggest that up to 27% of those with RAS develop chronic renal failure within 6 years. Importantly, several investigators have reported that renal artery revascularization is associated with stabilization or improvement in renal function.

The adverse effect of ischemia on the kidney is well established experimentally and clinically. The role of atherosclerotic RAS in the genesis of renal dysfunction is controversial, however. Over 1 to 4 years, atherosclerotic stenoses often progress, some to occlusion. RAS is associated with loss of renal size, a reasonable but crude measure of renal function. In patients with significant (>60%) RAS, 1 of 4 ipsilateral kidneys demonstrates atrophy of >1 cm in length, whereas significant loss of renal size is uncommon without RAS. Occlusion is associated with substantial loss of renal size and function.

Several investigators have been unable to demonstrate a relationship between stenosis severity and renal function. Although one might conclude from this finding that stenoses do not cause renal dysfunction, such a conclusion would be unfounded. Fundamentally, the kidney requires blood flow to function. Clearly, there are factors beyond percent stenosis that influence function. Some are intrinsic to RAS, including the duration of the insult, atheroemboli, hypertensive nephrosclerosis of the contralateral kidney, activation of the renin-angiotensin system, and effect of the stenosis (including lesion length, minimal lumen diameter, etc) on renal blood flow and intrarenal pressure. Additionally, other factors such as essential hypertension, diabetes, concomitant medications, generalized atherosclerosis progression, and aging play a role in determining overall renal function.

Most research has ascribed a direct role of the renin-angiotensin system in ischemic nephropathy. Angiotensin II induces efferent arteriolar constriction, which aids in the maintenance of glomerular filtration rate. Kidneys remain viable with blood flows and pressures below that required for glomerular filtration because <10% of oxygen delivery is required for kidney tissue metabolism. Thus, chronic ischemia does not damage renal tissue simply by lack of oxygen delivery. Chronic renal failure can be the result of severe global ischemia, but nephrosclerosis also occurs in the nonstenotic kidney, perhaps mediated by hypertension, a vasculotoxic effect of renin, or by angiotensin II through its interaction with endothelin-1, platelet-derived growth factor-β, and transforming growth factor-β. Gobe et al studied the cellular events related to unilateral RAS when the kidney underwent progressive atrophy. During the initial phase (2 to 5 days), tubular cell death resulted from both necrosis and apoptosis. During the later phase (10 to 20 days), renal atrophy progressed, and cell death resulted from apoptosis alone. After reversal of RAS, evidence of regeneration, consisting of hypertrophy and hyperplasia, was found. These findings imply that chronic ischemia is a dynamic process comprising not only an adaptation to reduced blood flow but also a potential for tubular cell regeneration.

RAS and Cardiovascular Events

In patients with RAS, the risk of cardiovascular morbidity and mortality appears to be substantial. Wollenweber et al described a 6-year cardiovascular event–free survival of 53%, with risk related to the severity of the renal stenosis. Several others have suggested that the risk of adverse cardiovascular events is high and occurs in excess of the severity of hypertension. More recently, a significant decrease in 4-year survival was seen in patients with incidental RAS undergoing coronary angiography. Thus, the risk of cardiovascular events appears to be high in RAS, and blood pressure control may be a poor surrogate for clinical outcomes.

It is not known whether the high cardiovascular event rate seen in patients with atherosclerotic RAS is attributable to the effects of renal ischemia and subsequent neuroendocrine activation or is simply a marker for advanced atherosclerosis and cardiovascular risk. A biologically plausible link is present, however, between renal ischemia and subsequent events that may be independent of blood pressure per se. Angiotensin II is implicated in smooth muscle proliferation, plaque rupture, endothelial dysfunction, and inhibition of fibrinolysis. Angiotensin II also promotes medial and cardiac myocyte hypertrophy. It is important to note that myocardial hypertrophy occurs when angiotensin II is present even when blood pressure is controlled. Angiotensin II interacts with other peptides like endothelin, transforming growth factor-β, and platelet-derived growth factor-β, each of which is implicated in end-organ damage, ventricular hypertrophy, and vascular hypertrophy.

Although the mechanism(s) responsible for the relationship between RAS and congestive heart failure (CHF) are not well characterized, there is little doubt that ventricular hypertrophy, sustained hypertension, activation of the renin-angioten-
sin and sympathetic nervous systems, and volume retention associated with renal ischemia are likely important contributors. Recent work suggests a relationship between brain natriuretic peptide and RAS, with high brain natriuretic peptide levels (>80 pg/mL) associated with better outcomes after renal artery intervention. Angiotensin II, endothelin, or an insulin-like growth factor, and sympathetic activation all may be involved in the process of ventricular thickening and stiffening. Angiotensin has been implicated in the mechanism of cardiac hypertrophy and is known to induce protein synthesis in myocardial cells, even when the mean arterial pressure is lowered. Endothelin also has been implicated in cardiac hypertrophy in RAS. Interestingly, the use of endothelin receptor blockers reverses left ventricular hypertrophy in rats with RAS.

Remodeling of the left ventricular wall and peripheral arteries in response to renovascular hypertension has been noted. In patients with RAS with hypertension, cardiac remodeling permits maintenance of normal cardiac function despite increased left ventricular wall stress resulting from systemic hypertension. Ventricular performance, determined by afterload, chamber size, mass index, and functional shortening or contractility, often is abnormal in people with renovascular hypertension.

Congestive heart failure is common in patients undergoing renal artery revascularization, just as RAS is common in patients presenting with CHF. Left ventricular hypertrophy and decreased contractility, risk factors for development of overt CHF, are significantly more common in those with renovascular hypertension than essential hypertension, even when matched for age and gender. RAS is prevalent in those with CHF and may be implicated in its cause or severity in a large proportion of patients. In a series of patients >70 years of age presenting with New York Heart Association class II to IV heart failure, 34% were found to have stenosis of at least 50% involving at least 1 renal artery.

As discussed, left ventricular hypertrophy is an important risk factor for cardiovascular events and cardiovascular death in both the presence and absence of hypertension. Regression of left ventricular hypertrophy is favorable prognostically, and left ventricular mass index, a measure of ventricular hypertrophy, has been shown to decrease after renal artery revascularization. When CHF accompanies RAS, renal artery revascularization often is associated with symptomatic improvement. Currently, this may be underrecognized in clinical practice. There certainly appears to be some confusion about the management of patients with RAS and CHF; the recent American Heart Association/American College of Cardiology consensus document on the management of peripheral vascular disease suggests limited support for screening patients with CHF but substantial support for treatment of RAS in patients with CHF, despite a paucity of evidence to support either position.

Limitations of Medical Therapy for RAS
Undoubtedly, all patients that have RAS require lifelong medical therapy to manage the underlying atherosclerotic process with statins, antiplatelet therapy, antihypertensive therapies, and hypoglycemic agents in the presence of diabetes. Inhibition of sympathetic activation and the renin-angiotensin-aldosterone system with β-blockers and angiotensin-converting enzyme inhibitors is a very successful strategy for patients with cardiovascular diseases in several settings, including acute myocardial infarction, CHF, and hypertension. In each of these settings, treatment has demonstrated significant benefits as measured by reductions in clinically important events. Renin-angiotensin-aldosterone system--inhibiting drugs also are indicated for retarding the progression to end-stage renal disease to preserve renal function. Although there are no outcome data with antihypertensive medical therapy for treatment of RAS specifically, clinical studies suggest that renin-angiotensin-aldosterone system inhibition decreases cardiovascular events in other high-risk patient groups.

Antihypertensive medical therapies can be associated with adverse health effects, however, such as lack of energy or chronic cough, which may affect quality of life and reduce compliance. Fifty percent to 70% of such medications are discontinued or changed within 6 months. Adherence to published guidelines for treatment of hypertension is poor, often with significant adverse impact on patients and the healthcare system. Other factors that may limit the effectiveness of medical therapy include temporal variations in drug levels and variable absorption. Finally, as described above, renal ischemia increases activity in a number of other pathogenic systems that may have deleterious cardiovascular or renal effects. Whether medical therapy alone is sufficient to minimize risk in patients with atherosclerotic RAS is not known.

Intervention Cohort Studies
An important feature of revascularization is the ability to obviate the root cause of the entire process: the stenotic renal artery. Importantly, others have demonstrated that relief of stenosis with revascularization results in a reduction in renin-angiotensin-aldosterone system and sympathetic activity. What is entirely unclear is whether pharmacological therapy directed at one or several of these pathways is equally effective or whether a reduction in activation attributable to revascularization leads to improvements in long-term clinical outcome.

In 1974, Hunt et al described lower rates of mortality, stroke, myocardial infarction, and azotemia and better blood pressure control in surgically revascularized patients than in a comparison medical group despite more severe hypertension in the revascularized subjects. Interestingly, in a more contemporary series comparing nonrandomized groups of patients with RAS and hypertension treated with stents or medications, Pizzolo et al reported a survival treatment effect in the intervention group similar to the experience of Hunt et al 30 years previously, with an 87% probability of
5-year survival in the intervention group versus 67% in the medical management group.

A number of single-center registries of stenting\textsuperscript{89} and a recent multicenter registry of stenting for failed balloon angioplasty\textsuperscript{90} suggest substantial benefits related primarily to improved blood pressure control. In contrast, the 3 multicenter trials of percutaneous balloon renal angioplasty (PTRA) without stenting failed to demonstrate a blood pressure benefit.\textsuperscript{91–93} Importantly, the randomized clinical trials done thus far have substantial weaknesses that have been the subject of considerable debate and discussion. The largest randomized trial comparing drug treatment and PTRA was the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study. In this study, 106 patients were randomly assigned to treatment by PTRA or medical therapy. The study design was such that refractory patients in the drug therapy group were allowed to receive balloon angioplasty if their blood pressure control was inadequate. With 44% of the drug therapy group receiving PTRA, the study contrasted provisional angioplasty against angioplasty. Despite the authors’ assertion that PTRA in addition to drug therapy provided “little benefit,” patients in the PTRA group were less likely to have deterioration of their blood pressure control or renal artery occlusion during 12 months of follow-up. Two other studies of balloon angioplasty versus medical therapy were confounded by similar issues and failed to demonstrate differences in blood pressure control.\textsuperscript{79,82} Importantly, none of the studies comparing PTRA and drug therapy thus far have included substantial numbers of patients who received stents.\textsuperscript{93} Renal artery stent placement is standard today and substantially improves technical and long-term clinical outcomes compared with angioplasty alone,\textsuperscript{89,94,95} especially for ostial stenoses,\textsuperscript{96} which make up 80% of atherosclerotic stenoses.\textsuperscript{97} In a meta-analysis of 1322 patients, stent placement had a higher technical success rate and a lower restenosis rate than did PTRA (98% versus 77% and 17% versus 26%, respectively; \(P<0.001\)) and a higher cure rate for hypertension.\textsuperscript{94}

**Limitations of Nonrandomized Evidence**

There is little controversy that stenting is an effective means of achieving durable revascularization of the renal artery. Similarly, there is a wealth of uncontrolled study data demonstrating that some patients receive substantial benefits in blood pressure control and renal function.\textsuperscript{89,94,98,99} However, renal function worsens in some individuals after revascularization, and blood pressure may not improve. The current controversy is driven by a singular key factor: the lack of an appropriate control group to allow the magnitude of the benefit derived from stenting to be measured. Does stent revascularization markedly reduce the risk of cardiovascular and renal events, does it modestly reduce events, or are the risks of stenting balanced or even overwhelmed by complications? This determination has fundamental implications in the decisions that physicians make. If stenting has substantial benefits, then screening programs for high-, moderate-, or potentially even low-risk individuals become advisable. In contrast, if the benefit is small or marginal, then screening and treatment may be reserved for those at high risk. Furthermore, identifying subsets that derive greater or lesser benefit or even harm becomes possible when the relative benefits and risks can be identified.

Undoubtedly, some patients with atherosclerotic RAS appear to have a very favorable response to revascularization as determined by improvement in blood pressure or kidney function. Previous investigators have suggested that the response to revascularization may be predicted by the presence of microvascular dysfunction measured with the renal resistive index\textsuperscript{100} or by the presence of neurohumoral activation.\textsuperscript{95} Fundamental though, each of these observations is limited by the absence of a contrasting group of medically managed patients who are concurrent and carefully controlled. Thus, all such observations suggest but are unable to establish the relative benefit of revascularization or the true value of the baseline test strategy to predict outcome with differing treatments. This limitation, the absence of a robust and appropriate control group, has led to false conclusions, later disproved with appropriate randomized trials, about the utility of a wide variety of clinical therapies, including surgery for Ménière’s disease,\textsuperscript{101} warfarin for acute myocardial infarction,\textsuperscript{102} portosystemic shunts,\textsuperscript{103} and antiarrhythmic therapy after myocardial infarction.\textsuperscript{104}

This is likely to be important for patients with renal artery hypertension. In fact, in the Scottish and Newcastle series,\textsuperscript{92} 55 patients with renovascular hypertension were randomized to angioplasty or medical therapy after a run-in period of 4 weeks. It was noted that significant decreases in blood pressure occurred before the initiation of treatment. Thus, the effect of revascularization on blood pressure, observed in cohort studies, may be confounded by regression to the mean.

**How Should Patients Be Managed?**

These issues have pragmatic implications for the various physicians who care for patients with ischemic renal disease. Many in the interventional community feel compelled to revascularize renal stenoses, even when found incidentally. In 2000, an estimated 19 800 renal angioplasties were performed for Medicare beneficiaries alone at an estimated cost of $200 million.\textsuperscript{105} From 1996 to 2000, the annual number of renal stent procedures has increased 364%.\textsuperscript{105}

In contrast, such enthusiasm is largely absent among nephrologists and others who routinely care for patients with chronic kidney diseases. Importantly, without widespread screening by the medical community, it is apparent that most patients with renovascular disease never come to attention. Recent work suggests that \(\approx 7\%\) of individuals \(>65\) years of age have significant RAS.\textsuperscript{106} Clearly, the majority are never identified within our communities, and far fewer are treated with either appropriate medical therapy or revascularization and medical therapy. This nihilistic approach of “no screen,
no treat” may be proximate to the occurrence of a number of preventable cardiovascular and renal events.

Is there an exit to this conundrum? Yes. The National Heart, Lung, and Blood Institute has funded a pivotal trial, Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), that is currently randomizing 1080 patients to optimal medical therapy versus optimal medical therapy with stenting, with a primary outcome consisting of a composite of attributable cardiovascular and renal events (www.coralclinicaltrial.org). At the present time, however, examining the published data provides little confidence that either intervention or medical management is superior for any given individual.

Conclusions

The case in favor of renal artery stenting is highly circumstantial but directionally consistent with important benefits of revascularization. Many of the physiological changes linked to adverse cardiovascular events may be improved with the durable relief of renal ischemia provided by stent therapy, including hypertension, sympathetic nervous system activation, oxidative stress, and direct hormone-mediated organ damage. In contrast, medication regimens may not be effective, and their use may be limited by side effects that influence compliance. Nonrandomized comparisons suggest superior survival with revascularization compared with medical therapy.18,87 The published randomized trials that have compared blood-pressure lowering between patients who are treated medically and those treated with renal artery angioplasty have shown no benefit of balloon angioplasty, a therapy of largely historical interest for the treatment of atherosclerotic RAS. The current debate about the role of medical therapy versus optimal medical therapy with stenting, with a primary outcome consisting of a composite of attributable cardiovascular and renal events (www.coralclinicaltrial.org). At the present time, however, examining the published data provides little confidence that either intervention or medical management is superior for any given individual.

Disclosures

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References

12. Anderson WP, Korner PL, Angus JA, Johnston CI. Comparison of stenting and medical therapy versus optimal medical therapy with stenting, with a primary outcome consisting of a composite of attributable cardiovascular and renal events (www.coralclinicaltrial.org). At the present time, however, examining the published data provides little confidence that either intervention or medical management is superior for any given individual.
Response to Cooper and Murphy

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Drs Cooper and Murphy admit that observational data are often misleading, citing several famous examples of therapies that initially appeared to be markedly beneficial but were found to be completely without value or even harmful when examined in randomized trials. Nevertheless, they go on to present several uncontrolled case series of patients with renal artery stenosis that appear to show a benefit of revascularization. These data should be viewed with skepticism and are at best hypothesis generating. The other main arguments in favor of revascularization are theoretical. Renal ischemia leads to a pattern of neurohumoral activation involving the renin-angiotensin-aldosterone system, the systemic nervous system, and other circulating mediators and cytokines. What is lacking, however, is evidence that revascularization reverses these changes and is more effective than medical therapy, which also blocks the same systems in this regard. In fact, there are many reasons why revascularization may not be effective. Most patients are elderly with advanced atherosclerotic disease in other vascular beds and end-organ damage, including cardiac hypertrophy, ischemic cardiomyopathy, myocardial fibrosis, hypertensive glomerular sclerosis, tubulointerstitial fibrosis, atheroemboli, and microcerebral and macrocerebral vascular disease. These changes are likely to drive adverse outcomes even if renal perfusion improves. Finally, the authors acknowledge that the 3 randomized controlled trials, albeit flawed, fail to demonstrate any advantage of angioplasty and stenting over medical therapy. If medical decision making is to be evidence based, then angioplasty and stenting should be rarely, if ever, performed.
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