Attending Rounds: A Patient with Accelerated Hypertension and an Atrophic Kidney

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Abstract
This case represents an individual with accelerating hypertension and declining kidney function associated with atherosclerotic renal artery stenosis. Key features include loss of GFR (reaching stage V CKD) during intensified antihypertensive drug therapy including agents that block the renin-angiotensin system and failure to appreciate the extent to which moderate renal artery stenosis was affecting his better kidney. Interpretation of duplex ultrasound studies was complicated by a discrepancy between near-normal peak systolic velocities and markedly abnormal segmental arterial waveforms. It was essential to recognize that both kidneys were abnormal and focus on recovery of perfusion to the better of these kidneys. Successful revascularization of one kidney allowed major improvement in GFR and BP control.


Case Summary
A 74-year-old retired businessman was referred for CKD stages 4 and 5 associated with an atrophic kidney, accelerated hypertension, and consideration for RRT, including renal transplantation. His history was notable for a remote history of smoking, hypertension for more than 25 years, and emergent surgical repair of a leaking abdominal aortic aneurysm 12 years previously.

During the previous 2 years, he was hospitalized two times for malignant phase hypertension. In one instance, he had transient facial and upper extremity weakness associated with arterial pressures of 240/125 mmHg. Symptoms improved as BP fell with therapy. Eight months later, he was readmitted with symptoms of encephalopathy and dyspnea, again with BP above 230/120 mmHg. Initial evaluation showed a small kidney (8.6 cm by ultrasound) on the right and a left kidney of normal size (12.5 cm). Serum creatinine had risen over this period from 1.3 to 2.5 mg/dl. It rose to 3.8 mg/dl over the 1 month before referral.

Renal arteriography 6 months ago showed a high-grade right renal artery stenosis (RAS) and moderate left RAS. An attempt at stenting the right renal artery was unsuccessful, attributed to severe atherosclerosis and vascular tortuosity.

Medications at this time included aliskiren, 150 mg every day; carvedilol, 25 mg two times per day; clonidine, 0.3 mg three times per day; minoxidil, 2.5 mg two times per day; valsartan, 160 mg two times per day; furosemide, 80 mg in a.m. and 40 mg in p.m.; aspirin, and darbepoetin-a, 60 mcg subcutaneously one time per week. He was also taking omeprazole, aspirin, clopidogrel, and vitamin D2.

Examination was remarkable for BP=146–182/70 mmHg and body mass index of 28.1. He was fully alert without neurologic deficits. Carotid, epigastric, and lower abdominal bruits were audible. Cardiac rhythm was regular with a fourth heart sound. A well healed abdominal scar was evident. There was a trace of edema.

Laboratory values included hemoglobin, 11.5 g/dl; hematocrit, 34%; white blood cell count, 4300; platelets, 92,000/μl; BUN, 57 mg/dl; sodium, 138 meq/L; potassium, 5.1 meq/L; bicarbonate, 29 meq/L; and chloride, 97 meq/L. Serum creatinine was 3.8 mg/dl, and eGFR was 14 ml/min per 1.73 m² (by the Chronic Kidney Disease Epidemiology Collaboration equation). Plasma renin activity was 1.9 ng/ml per hour; aldosterone was <4.0 ng/dl. Urinalysis showed normal microscopy and trace proteinuria.

Imaging
A magnetic resonance angiogram done elsewhere identified asymmetric kidney sizes and suggested signal disruption at the origin of both renal arteries (Figure 1). Angiography identified a high-grade stenosis of the right renal artery. The lesion at the origin of the left kidney was considered only moderate (Figure 2).

Case Discussion
This patient highlights several problems that converge for nephrologists and other clinicians caring for patients with RAS and widespread atherosclerotic disease, namely accelerating hypertension and declining kidney function. The specific questions prompting this referral focused on controlling BP and the potential benefits of either revascularization of the right smaller kidney and/or consideration of nephrectomy of a pressor right kidney. These concerns were reasonable issues considering the recent development of neurologic symptoms thought to reflect hypertensive encephalopathy. BP control was improved recently but tenuously achieved at the expense of a
complex regimen, including multiple drugs that block the renin-angiotensin system, vasodilators, α-β blockade, centrally acting sympathetic drugs, and loop diuretics. Not surprisingly, this patient was experiencing side effects related to fatigue, edema, and limitations on endurance and breathing, partly attributable to both drug therapy and/or, possibly, early uremic symptoms and anemia. Because of these symptoms, the patient himself was anxious to move forward with RRT. Clinicians at home had focused on the role of the smaller kidney but encountered technical limitations that prevented successful endovascular stenting.

What were the factors leading to rapidly accelerating hypertension? The urinalysis and laboratory studies were not suggestive of active parenchymal disease, and there was no evidence of outflow tract obstruction on ultrasound imaging. Review of his computed tomography imaging before his aneurysm repair confirmed that both kidneys had been of normal size and apparently symmetric function at that time. Hence, the unilateral loss of size in the presence of atherosclerotic disease likely reflects high-grade vascular occlusive disease of the main renal artery. With a normal urinalysis and known vascular disease, it is plausible that this individual had developed renovascular hypertension caused by atherosclerotic disease superimposed on longstanding essential hypertension. A relevant consideration is whether this patient has physiology more closely aligned with unilateral (one-clip-two-kidney renovascular hypertension) or bilateral (one-clip-one-kidney renovascular hypertension) as classically described. In the former case, removal of the pressor kidney as the primary source of renin release and activation of the sympathetic nervous system might reduce BP and the need for such a complex drug regimen. Against this formulation is the observation that initially measured levels of plasma renin activity in this patient were low. Unfortunately, the complex effects of drug therapy made interpretation of these values and underlying physiology difficult, specifically those effects related to the direct renin inhibitor (DRI), aliskiren, and the α-β blocking agent carvedilol. One cannot fault the clinicians for including renin-angiotensin-aldosterone system (RAAS) blockade in a patient like this patient. RAAS blockade has been associated with more effective BP control in renovascular hypertension than had been possible in the past, particularly with unilateral disease. Agents, such as angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), can be administered safely and are well tolerated in nearly 90% of RAS patients (1,2). According to registry and observational data, patients with RAS treated with these agents have more favorable clinical outcomes than patients treated without them. The role of the DRI aliskiren in RAS has not been completely characterized. Results of a prospective trial in essential hypertension combining DRI therapy with ARB suggest that a small additional pressure reduction may be achieved. Recent prospective
of perfusion averaging 35% that kidneys are highly perfused as part of their function as a filter and hence, use only a fraction of blood flow for metabolic requirements under normal conditions, unlike the heart or brain (4). These observations are consistent with treatment trials emphasizing the overall stability of kidney function during antihypertensive drug therapy. There are obvious limits to the ability to tolerate vascular occlusion. Severe reductions in blood flow eventually produce cortical ischemia and lead to atrophy and interstitial fibrosis. A renal scan was obtained in this patient showing markedly reduced function on the right (21% of total) compared with the left (79%). Although some filtration was preserved in the right kidney, it was a minor contributor to the total GFR under these conditions. The right kidney in this patient apparently had reduced blood flow long enough to lose both function and size, both of which limit the potential for recovery, even if BP can be successfully treated. It seems likely that these changes had developed over months and years.

What accounted for the progressive loss of GFR in this patient? I believe that clinicians in this setting must concentrate directly on the factors affecting the larger, more viable kidney (the left kidney in this case). Importantly, loss of a single kidney could not account for the rapid progressive loss of GFR developing over the several months before admission associated with a rise in creatinine from 1.5 to 3.8 mg/dl. Loss of an entire kidney after donor nephrectomy, for example, is associated with modest reduction in GFR. Serum creatinine is usually below 2.0 mg/dl, with mean eGFR exceeding 60 ml/min per 1.73 m² (5). To develop a rise in creatinine to 3.8 mg/dl in this case necessarily means that both kidneys are functioning poorly.

What exactly is the condition of the larger left kidney in this individual? As commonly observed, imaging studies indicated that some degree of RAS was present in this kidney also, although the size was well preserved. Renal artery duplex studies identified peak systolic velocities only in the range of 114 cm/s along the course of the renal artery. Is it possible that a separate renal abnormality is producing a loss of function, such as atheroembolic disease or malignant hypertension with fibrinoid necrosis? Perhaps a completely independent process or allergic drug reaction may be to blame? Urinalysis showed minimal proteinuria and no other evidence of an active parenchymal process. It should be apparent that the rise in creatinine was temporally associated with more intensive antihypertensive drug therapy, including intensified RAAS blockade. The capacity for GFR to become dependent on angiotensin II is a seminal observation and recognized to become physiologically active under specific conditions, including near-critical reductions in blood flow and sodium restriction (6,7). A rise in creatinine soon after starting ACE inhibitor/ARB therapy is a recognized clue to vascular compromise, sometimes from large-vessel occlusive disease and sometimes from small vessel disease as well (8). The work by Onuigbo (9) recommends withdrawal of ACE inhibitor/ARB therapy in most patients with otherwise unexplained progressive renal dysfunction to test this effect. Such a strategy is hard to

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ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
achieve in a patient like this patient with repeated episodes of malignant-phase hypertension. Observing this effect should prompt careful evaluation of the renal vasculature. In this case, review of duplex imaging provided additional critical insight. As shown in Figure 3, segmental arterial waveforms within the renal parenchyma indicate a delayed upstroke described as parvus tardus (10) associated with a relatively low resistive index (0.63). Parvus tardus has been described as characteristic of proximal arterial obstruction producing sufficient hemodynamic effect to delay transmission of the arterial pulse. The low resistive index suggests that the small vessels in the kidney remain able to accommodate forward blood flow in diastole. Although imperfect, these resistance data argue that intrarenal parenchyma damage associated with AKI, atheroembolic disease, or CKD from other processes had not yet produced widespread fibrosis in the renal microvasculature. This formulation is consistent with the relatively preserved cortical anatomy evident on both magnetic resonance and ultrasound examinations. It is important to note that delayed upstroke and parvus tardus waveforms seem to contradict the velocity measurements within the main renal artery. Renal duplex studies require considerable technical expertise and patience to define the entire vessel course. The reliability of such studies can be affected by body habitus (more difficult in obese patients), overlying tissue, and the experience of the operator. In our experience, high velocities in the appropriate vessel are rarely a false positive, but the potential to miss localized focal areas of stenosis is a definite risk. Hence, a negative duplex study can overlook focal lesions, which we suspected in this case. A small lesion affecting the proximal left renal artery was visible on magnetic resonance angiography and aortography but appeared to be minor.

A study using blood oxygen level-dependent (BOLD) magnetic resonance is illustrated for this patient in Figure 4. These images indicate that the small right kidney had widespread areas of hypoxia (i.e., elevated levels of deoxyhemoglobin), whereas the left kidney had lower levels in cortex with a normal-appearing gradient from the cortex to deeper segments of medulla. This normal distribution of oxygenation within the kidney is remarkably preserved in this individual, despite severely reduced GFR. Hence, we suspected that the recent deterioration of kidney function was most directly related to functional loss of filtration on the left and that kidney tissue itself was viable.

**Follow-Up**

This patient underwent renal angiography and endovascular stenting targeting the left kidney. A focal lesion at the origin was successfully stented. BPs, serum creatinine values, and medications are illustrated in Figure 5. Over subsequent months, lower BP levels were associated with progressive recovery of GFR, with serum creatinine levels falling to 1.3–1.5 mg/dl. Hemoglobin and electrolytes normalized. He continues to receive antihypertensive drug therapy, statins, and aspirin. There have been no additional neurologic events or other clinical hospitalizations. Angiotensin receptor blockade has been continued. Plasma renin activity was elevated after withdrawal of aliskiren.

**Discussion**

This case illustrates several important features related to atherosclerotic RAS in the current era. Successful management of aortic aneurysmal disease, for example, and other complications related to atherosclerosis is allowing more people to reach advanced age and develop other manifestations, such as bilateral RAS. Additionally, several prospective, randomized trials attempting to define the role of renal revascularization compared with current medical therapy have failed to identify compelling benefits to renal revascularization, which we and others have discussed.
These trials have been limited by enrollment of patients with less severe occlusive disease and undoubtedly confounded by the high rates of comorbid disease events that increase mortality in this population as a whole (13). Nonetheless, one effect of these negative trials has been to reduce the number of revascularization procedures in both Europe and the United States. In my view, this trend is an appropriate trend overall, because the enthusiasm for screening angiography and treatment of incidental RAS had been excessive. Overly aggressive intervention poses hazards associated with both costs and potential risks of invasive procedures, which most of us recognize as all too common. However, an additional result will almost certainly mean that more patients will present with advanced and progressive renovascular disease, like this patient. I believe that nephrologists will encounter more challenges of complex diagnostic testing, drug therapy, and invasive procedures in more complex renovascular disease than ever before. Failure to identify and reverse this process poses the risk of committing patients to RRT unnecessarily.

What are the key features that identify patients likely to gain from more intensive investigation and revascularization? Recognizing clinical syndromes signaling high-risk RAS is a major point, including episodes of flash pulmonary edema or like in this case, refractory hypertension and rapidly worsening renal function (14) (Table 1). Perhaps most important is recognizing the tempo of relatively rapid progression of both hypertension and renal dysfunction (i.e., weeks and months as opposed to years). Several reports indicate that recovery of renal function and BP benefits is correlated with relatively recent progression of vascular disease (15,16). How long is too long? One of the persistent unanswered questions in this disorder has been to reliably define kidneys in which revascularization is likely to restore function. As noted above, ultrasound

![Figure 4. Axial image slices from blood oxygen level–dependent MR for right and left kidneys.](https://example.com/image.png)

Left panel depicts the R2* map (reflecting the level of deoxyhemoglobin) of the right kidney, showing a hypoxic cortical zone and widespread areas of elevated deoxyhemoglobin in the medullary segments (red). Right panel depicts the R2* map in the left kidney, with a lower (blue) cortical zone and more gradual development of deeper medullary areas of hypoxia. This near-normal appearance of the corticomедullary oxygen gradient with the human kidney appeared despite reduced blood flow from renovascular occlusive disease (in the text).
measurements of resistive index and kidney size may be of value. These measurements have been difficult to confirm in any absolute way. Some have suggested that an index of kidney volume as determined by magnetic resonance with relatively reduced function by radionuclide scan may identify hibernating renal tissue (17). We have been impressed that advancing vascular occlusion does, indeed, produce cortical hypoxia at some point, which was illustrated using BOLD magnetic resonance in the right kidney (Figure 4); it activated inflammatory injury pathways with accumulation of macrophages, which is known to attract T lymphocytes within the renal parenchyma (18,19). In the past, Kaylor et al. (20) advocated for kidney biopsy before surgical renal artery bypass to identify kidney fibrosis and/or atheroembolic disease, although it has not been widely practiced. Recent reports indicate that technically successful revascularization can partially restore blood flow and relieve tissue hypoxia but regularly fails to reverse inflammatory signals identified by renal vein cytokine signatures (21). Hence, restoring blood flow may not reverse an active process of kidney injury in such cases, consistent with clinical reports in which a certain fraction of patients proceed on to continued loss of kidney function. We believe that such patients may benefit from adjunctive measures in the future, such as infusions of mesenchymal stromal/stem cell therapy to redirect inflammatory pathways to allow repair of microvessel and tubular injury, which has been observed in experimental models of renovascular disease (22). This area is an area of research that warrants additional work.

Summary
This case represents an individual with accelerating hypertension and declining kidney function associated with atherosclerotic renal artery stenosis. Key features include loss of GFR (reaching stage V CKD) during intensified antihypertensive drug therapy including agents that block the renin-angiotensin system and failure to appreciate the extent to which moderate RAS was affecting his better kidney. Interpretation of duplex ultrasound studies was complicated by a discrepancy between near-normal peak systolic velocities and markedly abnormal segmental arterial waveforms. It was essential to recognize that both kidneys were abnormal and focus on recovery of perfusion to the better of these kidneys. Successful revascularization of one kidney allowed major improvement in GFR and BP control.

Question and Answer Discussion
Vincent Canzanello, MD, Nephrology Staff Member: Interpretations differed between magnetic resonance, ultrasound, and angiographic imaging. How do you reconcile these differences and when should translesional gradient measurements be made?
S.C.T.: Integrating results regarding renal hemodynamics from imaging studies that provide different information is a challenge. Some clinicians distrust duplex ultrasound, often out of concern for operator dependence and variable expertise in their own institutions. Actually, measuring flow within the distal segments to identify tardus parvus waveforms and resistive index is less demanding than tracking velocities over the entire renal artery. Magnetic resonance angiography often overestimates vascular occlusion, because the images represent flow disruption rather than actual lumen. Measuring translesional gradients requires training and special equipment, but many interventional laboratories are so equipped—some would argue that revascularization cannot be justified if no gradient is present. Ultimately, the major determinant of imaging depends on the clinician’s level of suspicion and the commitment to intervene if a high-grade vascular occlusion is identified. The costs and potential hazards of invasive angiography usually delay this procedure until some other data are suggestive.
Sandra Herrmann, MD, Nephrology Fellow: Changes in serum creatinine appeared to develop rapidly. Could these changes have represented contrast-induced nephropathy?
S.C.T.: I agree that changes in this patient were relatively rapid, hence our interpretation that the tempo of change favored reversibility. I cannot exclude a role for contrast-induced nephropathy, but it usually recovers within days of exposure. Fortunately, arterial imaging often can be achieved with limited contrast (less than 80 ml) and saline infusion. Of greater concern was the possibility of atheroembolic disease, which is less often reversible. Let me emphasize that creatinine changes related to even moderate volume shifts, diuretic use, and/or RAAS blockade are magnified in the presence of renovascular disease. These changes likely reflect the kidney functioning near the limits of autoregulation of both blood flow and GFR beyond critical stenosis (23).

Michael McKusick, MD, Staff Member: BOLD magnetic resonance imaging is not yet widely available. What information did it provide in this case?

S.C.T.: This technique provides noninvasive, noncontrast mapping of tissue oxygenation, which was reflected by the levels of deoxyhemoglobin. The kidney is unique in its differential distribution of highly perfused (and oxygenated) cortex adjacent to less perfused medullary segments with a gradient of progressive hypoxia. Showed preserved cortical oxygenation and a normal cortical-medullary gradient in this case argued for a viable, perhaps hibernating (perfused but minimally filtering), left kidney and argued against atheroembolic disease or advanced cortical hypoxia (which was seen in the right kidney). Both of these findings suggested a salvageable left kidney that could recover function after stenting.

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References

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