Current Concepts

RENAL DYSFUNCTION COMPLICATING THE TREATMENT OF HYPERTENSION

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TREATMENT of hypertension in patients with normal renal function does not generally cause renal dysfunction. By contrast, in patients with hypertension and chronic renal insufficiency, it is not uncommon for the serum creatinine concentration to rise as the blood pressure is lowered. This complication is likely to be encountered more often since the guidelines governing adequate blood-pressure control have been made more stringent.\(^1\)\(^,\)\(^2\) For many physicians, the initial response to a deterioration in renal function is to decrease the dose of antihypertensive medications. This approach is based on the belief that the kidney has been affected by an adverse event related to aggressive lowering of the blood pressure. As the blood pressure increases, the physician is reassured because the serum creatinine concentration returns to the original base line. Unfortunately, such an approach is not optimal for the long-term preservation of renal function and should be discouraged. Rather, a small, nonprogressive increase in the serum creatinine concentration occurring in the context of better blood-pressure control should be viewed as indicating that the intraglomerular pressure has been successfully reduced. Allowing blood-pressure control to deteriorate in order to prevent a rise in the creatinine concentration can harm the very patients who benefit most from tight blood-pressure control, which has been proved to slow the progression of chronic renal failure. This decline in renal function is hemodynamic in origin and not secondary to structural injury to the kidney. The decline can be traced to changes in renal autoregulation that accompany chronic renal disease.

RENAL AUTOREGULATION

Normal renal autoregulation enables the kidney to maintain a fairly constant renal blood flow and glomerular filtration rate as the mean arterial pressure varies between 80 and 160 mm Hg.\(^3\) This process can be linked to two mechanisms that are intrinsic to the kidney: a myogenic reflex in the afferent arteriole and tubuloglomerular feedback. The myogenic reflex, which is intrinsic to the afferent arteriole, causes this vessel to either constrict or dilate in response to changes in intraluminal pressure. An increase in arterial pressure elicits a vasoconstrictive response, whereas decreased arterial pressure results in vasodilatation. Tubuloglomerular feedback serves to reinforce these changes in afferent tone by responding to changes in the distal sodium chloride concentration.\(^4\) Angiotensin II–mediated constriction of the efferent arteriole provides additional support for maintenance of the glomerular filtration rate when renal perfusion pressure decreases.

RENAL AUTOREGULATION IN CHRONIC HYPERTENSION

Under normal conditions, autoregulatory vasodilatation is maximal at a mean arterial pressure of approximately 80 mm Hg, so that with any further decline in blood pressure the glomerular filtration rate and renal blood flow will begin to fall in parallel. As the mean arterial blood pressure approaches the upper end of the autoregulatory curve, constriction of the preglomerular vessels is overcome by the high pressure, thus allowing more direct transmission of high systemic pressure into the glomerular circulation. The resultant high intraglomerular pressure can lead to glomerular injury and rapid loss of renal function.\(^5\)

In chronic hypertension, the small arteries of the kidney, including the afferent arteriole, undergo a number of pathologic changes that alter renal autoregulation.\(^6\) As with vessels elsewhere, the afferent arteriole initially shows evidence of endothelial dysfunction, leading to impaired vasodilatation. Over time, this impairment is exaggerated by the histologic changes of hyaline arteriosclerosis and myointimal hyperplasia. Functionally, these changes in vessel function and structure will be reflected by a rightward shift in the autoregulatory curve\(^7\) (Fig. 1). This shift is quite similar to the rightward shift in the autoregulatory curve of the cerebral circulation.\(^8\)\(^,\)\(^9\) The mean arterial pressure at which autoregulatory vasoconstriction gives way to pressure-induced forced vasodilatation is much higher as a result of these structural changes. Such changes may explain why certain patients tolerate chronically elevated blood pressure without having clinically evident renal disease.
Structural changes in the renal vasculature may initially have a protective role. Over time, however, progressive narrowing of the preglomerular vessels may result in ischemic injury, leading to tubular atrophy and interstitial fibrosis. With progressive renal injury, the autoregulatory capacity of the remaining vasculature becomes impaired in such a way that the intraglomerular pressure begins to vary directly with changes in the systemic arterial pressure. This change can be traced to a blunted capacity of the preglomerular circulation to either constrict or dilate in response to changes in the renal perfusion pressure. In essence, these vessels take on the characteristics of a passive conduit. In some patients, this impairment is so severe that a completely pressure-passive vasculature is present, in which any change in the mean arterial pressure is matched by a proportional change in the glomerular filtration rate. As a result, even moderate degrees of hypertension lead to exaggerated increases in the glomerular capillary pressure and to injury. Conceptually, one can view this change in renal autoregulation as if the normal sigmoidal relation between the intraglomerular pressure and the mean arterial blood pressure had become progressively more linear (Fig. 1). The impairment in renal autoregulation can explain why patients with chronic renal failure are more susceptible to accelerated loss of renal function if they also have uncontrolled hypertension.

Impairment of renal autoregulation can also explain why patients with hypertension and chronic renal failure are more likely to have an increase in the serum creatinine concentration when the blood pressure is lowered. A blunted ability of the preglomerular circulation to dilate in response to a drop in the mean arterial pressure will cause an exaggerated decrease in the intraglomerular pressure. This blunted vasodilatory response is probably the result of arteriolar hyalinosis and hypertrophy. These changes effectively raise the lower limit of renal autoregulation in subjects with chronic hypertension.

As a result, the glomerular filtration rate begins to decline at a blood pressure that would not affect renal function in a normal subject. In patients with normal base-line renal function, the decline in the glomerular filtration rate is usually not sufficient to cause an increase in the serum creatinine concentration. However, in patients with chronic renal failure, even small declines in the glomerular filtration rate will lead to an increase in the serum creatinine concentration. Such a decline in renal function is hemodynamic in origin and does not result from structural injury to the kidney. The decreased glomerular filtration rate simply reflects the fact that the blood pressure has
fallen below the lower limits of autoregulation. In many patients, this initial decline in renal function will either improve or resolve with long-term control of the blood pressure. This change can be traced to improvement in vessel structure and function, leading to a shift in the lower limit of renal autoregulation back toward normal. In patients whose renal function remains reduced, the long-term renal outcome is still improved by better blood-pressure control.2,19,21

Apperloo et al.19 assessed renal function in patients with mild-to-moderate renal insufficiency after they had received either an angiotensin-converting-enzyme (ACE) inhibitor or a beta-blocker. They then compared the long-term renal outcome in patients who had a large initial treatment-induced decline in the glomerular filtration rate with that in patients who had only a small initial decline. During a four-year follow-up period, renal function remained more stable in the patients with the largest initial decline in the glomerular filtration rate. In addition, in the same group, the glomerular filtration rate recovered nearly completely when therapy was discontinued at the end of four years, whereas no change occurred in the other group. The results were the same whether patients were treated with an ACE inhibitor or a beta-blocker. These data support the idea that an initial decline in renal function in patients with well-controlled blood pressure is functional and is associated with long-term renal protection. It is likely that a slight rise in the serum creatinine concentration in this setting serves as an indirect indicator that the intraglomerular pressure has been successfully reduced.

For example, a 52-year-old man with diabetic nephropathy and a baseline creatinine concentration of 1.8 mg per deciliter (159 µmol per liter) might have a blood pressure of 148/92 mm Hg. Treatment is started with an ACE inhibitor, and two weeks later the blood pressure has fallen to 138/82 mm Hg. The serum creatinine concentration is now 2.2 mg per deciliter (194 µmol per liter). Rather than discontinue the ACE inhibitor, potentially depriving this patient of an agent that can both slow the progression of chronic renal disease and provide long-term cardiovascular protection,2,22 the appropriate response is to continue the drug and recheck laboratory values in one week to ensure that the creatinine concentration has stabilized at the higher value. One should not view an increase of 20 to 30 percent in the serum creatinine concentration, which then stabilizes, as a contraindication to intensive blood-pressure control or, as in this case, to the use of an ACE inhibitor.

In patients with accelerated or malignant hypertension, treatment-induced reductions in blood pressure may precipitate renal failure severe enough to require the initiation of hemodialysis, particularly when the initial glomerular filtration rate is less than 20 ml per minute. Even this occurrence is not a contraindication to antihypertensive therapy, since control of blood pressure is needed to protect other vital organs, such as the brain and heart, whose function is not replaceable. In order to minimize hypoperfusion of vital organs, the blood pressure should be gradually lowered but eventually normalized. In some patients, sustained control of blood pressure may result in sufficient recovery of renal function that dialysis is no longer required.23,24

RENA L DYSFUNCTION AND SPECIFIC ANTIHYPERTENSIVE DRUGS

ACE Inhibitors

Renal dysfunction that accompanies antihypertensive therapy is a result of the lowering of blood pressure and is independent of the agent used. ACE inhibitors and angiotensin-receptor blockers are more commonly associated with this complication, since any decline in intraglomerular pressure due to blood-pressure lowering will be exaggerated by concomitant vasodilatation of the efferent side of the glomerular circulation. Decreased intraglomerular pressure and reduction of proteinuria are among the mechanisms that account for the renal-protective properties of these agents.25

In situations in which the initial increase in creatinine is greater than 30 percent or repeated measurements show a progressive increase, the appropriate response is to discontinue the ACE inhibitor and search for other causes of renal dysfunction. There are several conditions in which the use of ACE inhibitors may cause exaggerated or progressive declines in renal function (Table 1). The first involves substantial bilateral renal-artery obstruction (usually greater than 70 percent) or unilateral renal-artery obstruction in the case of a solitary functioning kidney. Under these conditions, increased tone of the efferent arteriole acts to attenuate the decline in intraglomerular pressure that results from the arterial obstruction. The tradeoff is that renal function and the glomerular filtration rate become dependent on sustained constriction of the efferent vessel by angiotensin II. A similar physiological response can occur in patients with polycystic kidney disease when the renal arteries are extrinsically compressed by large cysts.26 If the underlying obstruction cannot be treated, other classes of antihypertensive agents must be used.

ACE inhibitors can also cause an azotemic response when there is an absolute reduction in the intravascular volume (due to, for example, gastroenteritis, aggressive diuresis, or poor oral intake) or an effective reduction in the volume (due to, for example, moderate-to-severe congestive heart failure). In these settings, angiotensin II–mediated constriction of the efferent arteriole serves to minimize the decline in the
glomerular filtration rate that would otherwise occur as a result of the decrease in the renal perfusion pressure. In a patient with an absolute reduction in intravascular volume, the appropriate response is to withhold the ACE inhibitor and then resume treatment with the drug once the extracellular fluid volume has been replenished. In a patient with congestive heart failure, ACE inhibitors will increase the creatinine concentration when the decrease in intraglomerular pressure resulting from efferent vasodilatation is not offset by an increase in renal perfusion. This can occur in patients with severely depressed cardiac function, in whom a reduction in afterload can no longer increase cardiac output, or in patients undergoing aggressive diuresis.

A similar mechanism is responsible for renal dysfunction in patients given ACE inhibitors who are also receiving nonsteroidal antiinflammatory drugs (NSAIDs) or cyclosporine or who have early sepsis. These conditions are all associated with increased renal vasoconstriction. ACE-inhibitor–induced efferent vasodilatation in the face of decreased perfusion pressure accounts for the decline in the glomerular filtration rate.

In clinical practice, many of these factors are present at the same time. In a typical scenario, an elderly woman with normal baseline renal function and well-controlled blood pressure may be taking an ACE inhibitor and an NSAID for joint pain due to osteoarthritis. In the physician’s office she complains of poor oral intake and is found to have a community-acquired pneumonia. The serum creatinine concentration is 2.8 mg per deciliter (248 µmol per liter). The appropriate treatment for this patient is to withhold the ACE inhibitor and resume drug treatment only after the infection has been treated and the extracellular fluid volume has been restored. The NSAID should also be withheld and then resumed once renal function has returned to normal.

Angiotensin-Receptor Blockers

Angiotensin-receptor blockers can cause renal dysfunction by the same mechanisms as ACE inhibitors. The biology of angiotensin II and its receptors suggests that these adverse effects may be slightly less common than those caused by ACE inhibitors. Angiotensin-receptor blockers cause vasodilatation by blocking angiotensin II type 1 (AT1) receptors, which are located primarily on the efferent vessel. AT1 blockade is also associated with higher levels of angiotensin II, resulting in stimulation of angiotensin II type 2 (AT2) receptors, which are located primarily on the afferent side of the glomerular circulation. Stimulation of the AT2 receptor causes vasodilatation. Efferent vasodilatation (from blockade of AT1 receptors) combined with afferent vasodilatation (from stimulation of AT2 receptors) may allow the glomerular filtration rate to be better maintained in persons with decreased blood pressure. In animal models of volume depletion, angiotensin-receptor blockers have been shown to preserve the glomerular filtration rate better than ACE inhibitors. Whether such differences between angiotensin-receptor blockers and ACE inhibitors are sufficient to be of clinical relevance in maintaining renal function has not been well studied and, at present, should not be a factor in choosing between these two classes of drugs.

Diuretics

Diuretics are effective in achieving blood-pressure control in patients with hypertension. The use of low-dose thiazide diuretics in combination with ACE inhibitors usually does not lead to changes in renal function. By contrast, the use of loop diuretics in combination with ACE inhibitors can cause azotemia when the degree of diuresis exceeds the mobilization of edematous fluid to such a degree that the effective arterial blood volume decreases. One can minimize this complication by adjusting the dose of the loop diuretic in patients with edema so that the weight reduction does not exceed 1 kg per day.

Calcium-Channel Blockers

Calcium-channel blockers exert a vasodilatory effect on the afferent arteriole and are therefore less likely to cause a reduction in the glomerular filtration rate when the blood pressure is lowered. Although the maintenance of the glomerular filtration rate may be beneficial, afferent vasodilatation in a kidney with already impaired autoregulatory capacity will permit the systemic pressure to be transmitted more easily into the glomerular circulation and may accelerate the loss of renal function over the long term. Such effects may explain why amlodipine was associated with an adverse renal outcome in black patients with early hypertensive nephrosclerosis, even though it caused an initial increase in the glomerular filtration rate. Although all calcium-channel blockers dilate the afferent vessel, the disruption in renal autoregulatory control in patients with hypertension. The use of calcium-channel blockers in combination with ACE inhibitors usually does not lead to changes in renal function. By contrast, the use of loop diuretics in combination with ACE inhibitors can cause azotemia when the degree of diuresis exceeds the mobilization of edematous fluid to such a degree that the effective arterial blood volume decreases. One can minimize this complication by adjusting the dose of the loop diuretic in patients with edema so that the weight reduction does not exceed 1 kg per day.

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lution is less with nondihydropyridine calcium-channel blockers.\textsuperscript{37} This difference may explain, in part, why nondihydropyridine calcium-channel blockers are consistently associated with a beneficial effect on renal function; such benefit may be additive when these drugs are combined with an ACE inhibitor.\textsuperscript{2,41}

If a dihydropyridine calcium-channel blocker is to be given to patients with established nephropathy, it should be given with either an ACE inhibitor or an angiotensin-receptor blocker.\textsuperscript{2,41}

**Beta-Blockers and Other Classes of Antihypertensive Drugs**

Beta-blockers are effective agents for the treatment of hypertension in both diabetic and nondiabetic chronic renal disease.\textsuperscript{2,42} In the United Kingdom Prospective Diabetes Study of patients with type 2 diabetes, atenolol was as effective as captopril in terms of both blood-pressure lowering and protection against microvascular disease.\textsuperscript{42} In general, these drugs have no clinically important effects on renal hemodynamics and the glomerular filtration rate. They can cause the glomerular filtration rate to fall if the systemic blood pressure falls below the autoregulatory threshold. The $\alpha_1$-adrenergic agonists and $\alpha_1$-adrenergic antagonists are similar in this regard.

**HYPERKALEMIA AS A COMPLICATION OF ANTIHYPERTENSIVE THERAPY**

The use of ACE inhibitors or angiotensin-receptor blockers in patients with chronic renal disease can be associated with hyperkalemia. As with an increase in the serum creatinine concentration, many physicians respond to even mild increases in a patient’s serum potassium concentration by immediately discontinuing the ACE inhibitor or angiotensin-receptor blocker. In many instances, physicians are reluctant even to initiate therapy with these drugs simply because the patient has an elevated creatinine concentration. Such an approach is to the patient’s disadvantage, because these drugs provide more protection from the progression of renal disease in patients with more advanced renal insufficiency.\textsuperscript{21} Although close monitoring is required, several steps can be taken to minimize the likelihood of hyperkalemia (Table 2).

One should review the patient’s medication profile and, whenever possible, discontinue drugs that can impair renal potassium excretion. NSAIDs, either prescription or over-the-counter drugs, are common offenders in this regard.\textsuperscript{43} The patient should be placed on a low-potassium diet, with specific counseling against the use of potassium-containing salt substitutes. Diuretics are particularly effective in minimizing hyperkalemia. Thiazide diuretics can be used in patients with serum creatinine concentrations of less than or equal to 1.8 mg per deciliter, but loop diuretics are required in cases of severe renal insufficiency. In patients with chronic renal failure and metabolic acidosis (bicarbonate concentration, less than 20 mmol per liter), sodium bicarbonate should be given. Decreasing the dose of the ACE inhibitor or switching to an ACE inhibitor that is not totally dependent on renal excretion may help. In one study of patients with mild chronic renal failure, an angiotensin-receptor blocker increased the serum potassium concentration less than an ACE inhibitor.\textsuperscript{44} However, the difference was small, and at present these agents should be viewed as involving similar risks of hyperkalemia.

With implementation of these steps, the risk of hyperkalemia severe enough to warrant discontinuation of ACE inhibitors or angiotensin-receptor blockers is quite low, even in patients with moderate-to-severe renal insufficiency. In patients with chronic renal disease, the serum potassium concentration should be checked within one or two weeks of starting therapy with an ACE inhibitor or an angiotensin-receptor blocker. If the potassium concentration increases above 5.6 mmol per liter despite the precautions noted above, another class of antihypertensive drugs must be chosen.

**Table 2. Steps to Minimize Hyperkalemia Induced by Angiotensin-Converting–Enzyme Inhibitors and Angiotensin-Receptor Blockers.**

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<thead>
<tr>
<th>Step</th>
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<tr>
<td>Discontinue drugs known to interfere with renal potassium secretion</td>
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<tr>
<td>Prescribe a low-potassium diet</td>
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<tr>
<td>Use thiazide or loop diuretics*</td>
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<tr>
<td>Use sodium bicarbonate to treat metabolic acidosis</td>
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<tr>
<td>Decrease the dose of angiotensin-converting–enzyme inhibitor or use an angiotensin-converting–enzyme inhibitor with a component of hepatic excretion</td>
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*Loop diuretics are necessary when the creatinine concentration is above 1.8 mg per deciliter.

Dr. Palmer reports having lectured on behalf of Novartis, Pfizer, and Merck.

**REFERENCES**


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