



# Control of hypertension in patients with chronic renal failure

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■ Hypertension related to renal parenchymal disease is the most common cause of secondary hypertension. Poor control of renal hypertension is associated with an increased risk for progressive atherosclerosis and progressive renal failure. This review discusses the prevalence, significance, and pathophysiology of renal hypertension. Treatment options, both dietary and pharmacologic, are reviewed. Special emphasis is given to important pharmacokinetic changes in chronic renal failure. Treatment of hypertensive urgencies and emergencies in this population is also reviewed.

□ INDEX TERMS: HYPERTENSION; KIDNEY DISEASES □ CLEVE CLIN J MED 1989; 56:65-76

**H**YPERTENSION and chronic renal failure may be related in one of two ways. First, essential or idiopathic hypertension may cause renal parenchymal damage. The kidney may be more victim than culprit in this situation. It is important to break the cycle of idiopathic hypertension with adequate control of the hypertension, thus preventing progressive renal damage. Second, chronic renal failure is frequently accompanied by hypertension. Here the kidney may be more the culprit but is also a victim of its own dysfunction. Hypertension secondary to chronic renal failure presents certain unique challenges to the clinician. We will consider several important aspects of this latter association, including differences in prevalence with various renal diseases, risks associated with deteriorating renal function and atherosclerosis, as well as pathogenesis and treatment.

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## PREVALENCE AND VARIATION

Chronic renal disease is the most common cause of secondary hypertension accounting for 2.5% to 5% of all hypertension. Renal parenchymal hypertension is more prevalent than the hypertension due to renovascular disease or endocrine abnormalities such as Cushing's syndrome, primary hyperaldosteronism, or pheochromocytoma, which account for 0.5% to 3% of all hypertension.<sup>1</sup>

A recent study compared 3,090 determinations of glomerular filtration rate (GFR) using the isotope iothalamate I-131 with the corresponding serum creatinine levels. In patients aged 41 to 50 years, a GFR of 50 mL/min/1.73 m<sup>2</sup> was seen with an average serum creatinine value of 1.5 mg/dL in females and 1.7 mg/dL in males. With a GFR of 25 mL/min/1.73 m<sup>2</sup>, the average serum creatinine values were 2.2 and 2.8 mg/dL, respectively. In patients aged 61 to 70 years, the serum creatinine value averaged 1.2 and 1.6 mg/dL for females and males with a GFR of 50 mL/min/1.73 m<sup>2</sup> (Hall P, unpublished data).

Thus the serum creatinine value can be falsely reassuring, and significant renal failure can be present even

**TABLE 1**  
PREVALENCE OF HYPERTENSION AND ETIOLOGY OF CHRONIC RENAL FAILURE\*

|                                                     |
|-----------------------------------------------------|
| Common                                              |
| Vascular disease                                    |
| Systemic lupus erythematosus                        |
| Scleroderma                                         |
| Polyarteritis                                       |
| Glomerular disease                                  |
| Postinfectious (short-lived) glomerulonephritis     |
| Crescentic (rapidly progressive) glomerulonephritis |
| Focal segmental glomerulosclerosis                  |
| Diabetic nephropathy                                |
| Tubo-interstitial disease                           |
| Autosomal dominant polycystic kidney disease        |
| Analgesic abuse nephropathy (geographic variation)  |
| Uncommon                                            |
| Membranous glomerulonephritis                       |
| Membrano-proliferative glomerulonephritis           |
| IgA nephropathy                                     |
| Chronic pyelonephritis                              |

\*Data derived from Blythe<sup>2</sup> and McDonald.<sup>3</sup>

with modest increases in serum creatinine levels.

The prevalence of hypertension in patients with chronic renal failure varies with the etiology and severity of the renal disease (Table 1). Diseases that involve the small renal vessels, including systemic lupus erythematosus, scleroderma or vasculitis, and certain glomerulopathies such as diabetic nephropathy and rapidly progressive glomerulonephritis (RPGN), are associated with rates of hypertension approaching 90%–100% in patients with end-stage renal failure.<sup>4</sup> In postinfectious glomerulonephritis, hypertension occurs in approximately 75% of patients but is transient, lasting an average of one to six weeks. In other disorders, such as vasculitis or RPGN, the hypertension persists and significantly worsens the renal damage if not controlled. Among renal disorders associated with tubular or interstitial diseases, autosomal dominant polycystic kidney disease and analgesic-abuse nephropathy are frequently complicated by hypertension, with a prevalence reported between 40% and 75%.<sup>2</sup> An important consideration is that both the incidence and severity of hypertension worsen with chronic renal failure of any etiology as renal function deteriorates. The overall prevalence rate of hypertension approaches 80% in predialysis patients.<sup>5</sup>

#### SIGNIFICANCE AND SURVIVAL

##### Atherosclerosis

Chronic renal failure may itself be a risk factor for atherosclerosis—so called “accelerated atherosclerosis.”<sup>6</sup>

This concept is still disputed and several authors have found no risk from chronic renal failure that is independent of other known risk factors.<sup>7,8</sup> Nevertheless, atherosclerotic cardiovascular disease is the most common cause of death in patients with chronic renal failure. Many factors can potentially contribute to this problem.<sup>9</sup> As with any patient at risk for atherosclerotic disease, patients with chronic renal failure should be strongly encouraged to discontinue tobacco use, lipids should be regularly monitored, and dietary or pharmacologic treatment should be initiated if necessary. Glucose levels should be tightly controlled in patients with insulin-dependent diabetes mellitus. Of all the potential atherosclerotic risk factors in patients with chronic renal failure, hypertension is probably the most important.<sup>10,11</sup> This emphasizes the need for aggressive and adequate control of blood pressure in patients with chronic renal failure.

##### Progression of renal failure

The second major consideration for treatment of hypertension is related to prevention of progressive renal damage. In many instances, progression to end-stage renal disease occurs despite the spontaneous or therapeutic resolution of the initial renal insult. Worsening renal function can be seen in such diverse disorders as acute tubular necrosis, analgesic nephropathy, vesicoureteral reflux, and post-streptococcal glomerulonephritis, even with adequate treatment of the primary renal problem.<sup>12</sup> Once a critical percentage of renal function is lost (approximately 80%), progression to end-stage renal disease with need for dialysis or transplantation is very likely, regardless of the initial renal insult.<sup>13</sup>

##### How does treatment of hypertension help preserve renal function?

In the past, it was thought that renal arteriolar constriction and vascular sclerosis (as is seen with malignant hypertension) were the major pathologic mechanisms in the continued destruction of renal tissue. Emphasis has recently shifted to the concept that it is the transmission of increased hemodynamic pressures and flows to the glomerular vessels that is a major mechanism in continued renal damage.<sup>14</sup> Particular agents, especially angiotension-converting enzyme (ACE) inhibitors, may have a more beneficial effect on preservation of residual glomerular function than other antihypertensive agents. By decreasing efferent arteriolar constriction, these agents reduce intraglomerular pressures and thus may offer protection for the damaged kid-

ney.<sup>15</sup> It is argued that this protection may be lacking with "nonspecific" control of systemic blood pressure unless intraglomerular pressures are also lowered. Several studies have shown a protective effect against progression of renal damage with use of "nonspecific" agents. In one dietary study, patients enrolled in the control phase had slowed progression of chronic renal failure simply with more frequent office visits and better control of blood pressure.<sup>16</sup> This occurred independent of any dietary protein restriction. The antihypertensive drugs used were diuretics, as well as other nonspecified agents.

Although hypertension in chronic renal disease is only a single factor in the progression of chronic renal failure,<sup>17,18</sup> multiple studies have shown its significance if uncontrolled. Unresolved issues include minimum reductions in blood pressure that are necessary to protect the kidney and whether even further reduction in blood pressure would be helpful or harmful. Also, the questions of systemic *v* intraglomerular pressure control and the potential benefit of specific agents remain to be answered. Studies are underway to determine the benefits of different agents in renal hypertension, and clarification of these issues should be forthcoming.

#### **PATHOPHYSIOLOGY**

The pathophysiology of hypertension in this setting is truly multifactorial.<sup>19</sup> There is currently much discussion about the initiating events in renal parenchymal hypertension and whether a hyperdynamic state with increased cardiac output precedes the established state.<sup>20</sup> There is general agreement, however, that the "marker" of established renal parenchymal hypertension is increased total peripheral resistance.<sup>2</sup> This hemodynamic finding has important clinical consequences in the choice of antihypertensive therapy as drugs that act to decrease total peripheral resistance are usually the most effective agents.

#### **Sodium/water**

In a study of patients with mild chronic renal failure (GFR,  $59 \pm 29$  mL/min/1.73 m<sup>2</sup> and creatinine values,  $2.0 \pm 1.1$  mg/dL), there were several important findings. Hypertension was inversely related to GFR and renal plasma flow and directly related to total duration of hypertension. There was no clear-cut relation between blood pressure and either blood volume or plasma renin activity when each was considered independently. Only the product of total exchangeable sodium (NaE) and plasma renin activity or blood volume and plasma renin

activity showed significant correlation with hypertension. The best correlation was with hypertension and the product of duration of hypertension, plasma renin activity, and either NaE or blood volume, demonstrating the interdependent roles played by sodium, fluid status, circulating renin, and the duration of hypertension.<sup>19</sup>

An interesting and unsettled question is whether the relation between sodium/volume and elevated blood pressure is a direct one via volume expansion and an increased cardiac output or an indirect one mediated by other pressor mechanisms. In the latter situation, sodium would function as a marker of volume or as a possible inducer of other pressor mechanisms but not as a direct factor in the genesis of hypertension.<sup>21</sup> Blaustein and Hamlyn<sup>22</sup> have suggested a link between sodium retention, intracellular calcium, and natriuretic hormone in essential hypertension and called it the "natriuretic hormone/sodium-calcium exchange/hypertension hypothesis." This hypothesis relates impaired sodium excretion with secretion of a hypothalamic-produced factor and was initially postulated in studies of uremic patients.<sup>23</sup> Natriuretic hormone would usually decrease sodium reabsorption in the renal tubule and promote natriuresis in states of sodium and volume excess. This hormone may have an ouabain-like effect on the cell membrane sodium-potassium ATPase pump and exert an influence on the resting state and responsiveness of all cells, including neurons and vascular smooth muscle. To what extent natriuretic hormone is present and active in patients with chronic renal failure remains to be determined.

Whatever the exact pathophysiologic role(s) of sodium and volume in the genesis and maintenance of renal hypertension, there is little debate over the necessity of controlling sodium and water status during treatment.

#### **Renin-angiotensin-aldosterone axis**

The renin-angiotensin-aldosterone (RAA) axis remains functional in chronic renal failure. Appropriate increases are seen with low-salt diets, orthostatic changes, and volume depletion with diuretics or dialysis.<sup>4</sup> Plasma renin activity levels vary over a wide range in patients with chronic renal failure. If 5 ng/mL/hr is used as an upper limit, approximately 30% of patients with chronic renal failure will have levels above this value.<sup>24</sup> Although an inverse relationship continues between NaE and plasma renin activity, plasma renin activity levels are inappropriately elevated for the level of NaE when compared to patients without renal failure.<sup>25</sup> In addition, extra-renal production of renin and angio-

**TABLE 2**  
CONSIDERATIONS IN THE TREATMENT OF RENAL PARENCHYMAL HYPERTENSION

#### General

- Should be viewed as part of overall cardiovascular risk profile
- Probably the most important factor in progression of chronic renal failure
- Incidence increases as GFR decreases
- Serum creatinine level may not accurately reflect GFR or changes in GFR
- Start with small doses
- Be prepared to change medicines, total doses, and timing of doses as GFR decreases
- Be aware of drug interactions (sodium bicarbonate, phosphate binders, NSAIDs)

#### Dietary

- Start with moderate salt restriction (1500–2000 mg/d)
- There is impaired ability to adapt to rapid changes in salt intake
- Dietary changes become inadequate as GFR and filtered load of sodium decrease
- Potassium supplements must be used cautiously, if at all

#### Diuretics

- Maintenance of “dry weight” controls hypertension in many patients
- Avoid thiazides when creatinine level is  $>2.5$  mg/dL (GFR  $<30$  mL/min)
- Avoid potassium-sparing agents
- Loop diuretics alone or in combination with thiazides (metazone) are most potent agents
- Volume removal may increase potency of other agents (ACE inhibitors, central agonists, vasodilators)
- “Pseudotolerance” to medications may develop if volume status not controlled

#### Second-line drugs

- If salt and water retention are not problems, some agents may be used as first-line drugs
- Within classes of agents, pharmacokinetics of individual drugs differ significantly.
- Associated medical problems such as diabetes mellitus, chronic obstructive pulmonary disease, arteriosclerotic heart disease, orthostatic hypotension, depression, and vascular disease will often dictate the choice of agent(s).
- Certain agents may have theoretical advantages for preservation of renal function.

otensin II has been described in vascular and central nervous system locations.<sup>26</sup> Local production and activity of angiotensin II probably plays a part in the hypertension of chronic renal failure. The strongest evidence for the role of the RAA axis in renal hypertension is that several studies have shown both converting enzyme inhibitors and the angiotensin antagonist saralasin to be effective in controlling blood pressure in most patients.<sup>24</sup>

#### Autonomic nervous system

The exact role of the autonomic nervous system in the pathogenesis of hypertension is still unclear.<sup>27</sup> As with NaE and plasma renin activity, there may be altered end-organ sensitivities to catecholamines and a spectrum of autonomic nervous system responsiveness in patients with chronic renal failure.<sup>28</sup> An impairment in the afferent limb low-pressure baroreceptors exists in many patients with chronic renal failure<sup>29</sup> and can lead to autonomic instability, especially with vigorous treatment of hypertension.

#### TREATMENT

Since chronic renal failure is a multi-organ disorder, it is not surprising that there are derangements in many

homeostatic mechanisms. Metabolic acidosis, secondary hyperparathyroidism, alterations in lipoprotein pathways, and abnormalities secondary to continued therapy of underlying renal disease with steroids or cytotoxic agents can all complicate the picture. Important considerations in the treatment of hypertension with chronic renal failure are outlined in *Table 2*. As mentioned, uncontrolled hypertension may be the most important factor in the progression of chronic renal failure, as well as the progression of atherosclerotic disease. However, hypertension is only one part of the overall cardiovascular risk profile and other abnormalities should be aggressively treated as well.

#### Nonpharmacologic therapy

Initial dietary treatment of hypertension and chronic renal failure involves attainment and maintenance of dry weight by restriction of water and sodium intake. Dry weight is that weight at which there is no clinical evidence of volume overload, such as edema, and below which further attempts to decrease weight lead to signs and symptoms of dehydration.<sup>27</sup> Dry weight is usually determined clinically, but radionuclide determination of plasma volume may be necessary at times.

Most patients are able to markedly increase their frac-

**TABLE 3**  
ANTIHYPERTENSIVE AGENTS AND DOSING INFORMATION IN CHRONIC RENAL FAILURE

| Drug                                                               | Dosage range*<br>(mg/d)<br>(normal renal<br>function) | Adjustment<br>with renal<br>failure                                                         | Precautions                                                                                                                                                       |
|--------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Diuretics</b>                                                   |                                                       |                                                                                             |                                                                                                                                                                   |
| Thiazides                                                          |                                                       |                                                                                             |                                                                                                                                                                   |
| Hydrochlorothiazide                                                | 12.5–50                                               | None with GFR >30 mL/min                                                                    | Avoid if GFR <30 mL/min; volume depletion; hypokalemia; diuresis required for effect                                                                              |
| Metolazone                                                         | 1.25–10                                               | None<br>Effective to GFR<br>approximately 10 mL/min                                         |                                                                                                                                                                   |
| <b>Loop Agents†</b>                                                |                                                       |                                                                                             |                                                                                                                                                                   |
| Bumetanide                                                         | 0.5–5                                                 | None                                                                                        | Volume depletion; hypokalemia; interstitial nephritis; ototoxicity; diuresis required for effect                                                                  |
| Furosemide                                                         | 20–320                                                | None                                                                                        |                                                                                                                                                                   |
| Ethacrynic acid                                                    | 25–100                                                | None                                                                                        |                                                                                                                                                                   |
| <b>Potassium-sparing agents (usually in combination diuretics)</b> |                                                       |                                                                                             |                                                                                                                                                                   |
| Amiloride                                                          | 5–10                                                  | Major dosage reduction                                                                      | Hyperkalemia if GFR <30 mL/min                                                                                                                                    |
| Triamterene                                                        | 50–150                                                |                                                                                             |                                                                                                                                                                   |
| Spironolactone                                                     | 25–100                                                |                                                                                             |                                                                                                                                                                   |
| <b>Beta blockers</b>                                               |                                                       |                                                                                             |                                                                                                                                                                   |
| Acetazolol                                                         | 200–1200                                              | Accumulation of diacetolol<br>(active)<br>Half dose if GFR 25–50<br>Quarter dose if GFR <25 | Accumulation of active parent compound and metabolites                                                                                                            |
| Atenolol                                                           | 25–150                                                | Same                                                                                        | Same                                                                                                                                                              |
| Nadolol                                                            | 40–320                                                | Same                                                                                        | Same                                                                                                                                                              |
| Metoprolol                                                         | 50–200                                                | None                                                                                        | —                                                                                                                                                                 |
| Pindolol†                                                          | 10–60                                                 | None                                                                                        | —                                                                                                                                                                 |
| Propranolol†                                                       | 40–320                                                | None                                                                                        | Accumulation of glucuronide metabolites. Activity unknown                                                                                                         |
| Timolol†                                                           | 20–80                                                 | None                                                                                        | —                                                                                                                                                                 |
| Labetalol†                                                         | 200–1800                                              | None                                                                                        | —                                                                                                                                                                 |
| <b>Alpha blockers</b>                                              |                                                       |                                                                                             |                                                                                                                                                                   |
| Prazosin†                                                          | 1–20                                                  | Probably requires lower doses                                                               | First dose effect<br>Start with low doses<br>Prolonged hypotension                                                                                                |
| Terazosin                                                          | 1–20                                                  | Same                                                                                        | Same                                                                                                                                                              |
| Labetalol                                                          | See Beta-blockers                                     |                                                                                             |                                                                                                                                                                   |
| <b>Central Agents</b>                                              |                                                       |                                                                                             |                                                                                                                                                                   |
| Methyldopa†                                                        | 250–2000                                              | Active metabolites accumulate<br>Half dose if GFR <20<br>Half dose if GFR <10               | Pseudohypertension; increased effects with volume depletion; orthostatic hypotension                                                                              |
| Clonidine†                                                         | 0.1–1.2                                               | None                                                                                        |                                                                                                                                                                   |
| Guanabenz†                                                         | 4–64                                                  | None                                                                                        |                                                                                                                                                                   |
| Guanfacine                                                         | 1–3                                                   | None                                                                                        |                                                                                                                                                                   |
| <b>ACE inhibitors</b>                                              |                                                       |                                                                                             |                                                                                                                                                                   |
| Captopril†                                                         | 25–300                                                | Half dose if GFR 20–50<br>Quarter dose if GFR <10                                           | Increased incidence of side effects with decreased GFR; rash; leukopenia; dysgeusia; hyperkalemia; acute renal insufficiency with bilateral renal artery stenosis |
| Enalapril                                                          | 2.5–40                                                | Same                                                                                        |                                                                                                                                                                   |
| Lisinopril                                                         | 5–40                                                  | Same                                                                                        |                                                                                                                                                                   |
| <b>Calcium channel blockers</b>                                    |                                                       |                                                                                             |                                                                                                                                                                   |
| Diltiazem†                                                         | 60–360                                                | None                                                                                        | Constipation                                                                                                                                                      |
| Nifedipine†                                                        | 30–180                                                | None                                                                                        | Hemodynamic worsening of renal function                                                                                                                           |
| Verapamil†                                                         | 120–480                                               | None                                                                                        | Constipation                                                                                                                                                      |
| <b>Vasodilators</b>                                                |                                                       |                                                                                             |                                                                                                                                                                   |
| Hydralazine†                                                       | 50–300                                                | Increase dosage with GFR <10                                                                | Sodium and fluid retention<br>Reflex tachycardia<br>Prolonged hypotension                                                                                         |
| Minoxidil†                                                         | 2.5–80                                                | None                                                                                        | As above                                                                                                                                                          |
| Diazoxide                                                          |                                                       | Lower and slower doses                                                                      | Decreased protein binding<br>May precipitate angina<br>Prolonged hypotension                                                                                      |
| Nitroprusside                                                      |                                                       | Limit infusion times                                                                        | Neurologic abnormalities:<br>Hyperreflexia<br>Confusion<br>Seizures<br>Thiocyanate toxicity<br>Monitor levels                                                     |

\* Dosage ranges taken from the 1988 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.<sup>32</sup>

†Requires multiple doses per day.

tional excretion of sodium (FENa) as the GFR decreases. FENa must double for each 50% fall in GFR to maintain balance.<sup>30</sup> However, the renal response to rapid increases in sodium intake is blunted with chronic renal failure, and this heightens the risk for acute fluid overload with dietary indiscretion. Similarly, the risk for dehydration with rapid or severe salt restriction exists, although with gradual decrease in sodium intake most patients can undergo “de-adaptation” and maintain sodium balance.<sup>31</sup>

Reasonable starting guidelines for sodium are 1,500 to 2,000 mg per day with a fluid intake to match urine production plus an allowance of approximately 500 mL for insensible losses. There is certainly a trade-off, as the more severe the fluid and sodium restriction, the less likely is continued good compliance. As the GFR decreases, dietary therapy becomes ineffective and other treatment modalities must be added.

### Pharmacologic therapy

Important considerations in the choice of pharmacologic agents include the site(s) of metabolism, the presence and activity of metabolites, and changes in the half-life and protein binding of parent compound and metabolites with worsening renal function. It is not uncommon for patients with chronic renal failure to have associated medical conditions that must also be considered in the treatment of hypertension. Examples include diabetes mellitus, coronary artery disease, peripheral vascular disease, and lipid abnormalities. Pharmacologic information useful in the choice and proper dosing of antihypertensive agents in chronic renal failure is presented in *Table 3*.

**Diuretics.** Given the central role of sodium in the pathophysiology of hypertension with renal disease, either directly with increased extracellular fluid or indirectly via other vasopressor mechanisms, pharmacologic therapy for renal hypertension usually begins with diuretics. These agents produce a diuresis and natriuresis and thus decrease extracellular fluid volume. They can cause a mild decrease in GFR and renal blood flow, especially with overly vigorous diuresis.<sup>33</sup> However, with proper dosing, neither volume depletion nor reduction in renal function is seen, even with long-term use.<sup>34</sup> The extracellular fluid volume tends to return toward normal and chronic effects probably include a decrease in peripheral resistance.

**Thiazides.** Thiazide diuretics are useful agents when the GFR is greater than 30 mL/min (serum creatinine value <2.5 mg/dL). Hydrochlorothiazide at 25 to 50 mg/day or chlorthalidone in equivalent doses is the usual

agent. Once the GFR falls below 30 mL/min, three factors act to decrease the effectiveness of thiazide diuretics:

1. Less sodium is filtered and thus less sodium reaches the distal tubules where thiazides act.

2. The proximal tubular organic ion transport system, which is necessary to transport thiazides into the lumen where they are active, is less effective in chronic renal failure since other organic and inorganic anions, such as ketoacids, phosphates, and urates, compete with thiazide secretion, a problem which also occurs with loop diuretics.

3. More avid reabsorption of sodium and chloride occurs in the medullary thick ascending loop of Henle proximal to the site of action of thiazide diuretics. (This is, however, the site of action of loop diuretics.)

As a result, less total administered dose of medication arrives at the site of activity at the same time that higher doses of medication are required due to decreased filtered load of sodium. Although as mentioned previously, “adaptive natriuresis” does occur with chronic renal failure, as the GFR declines, use of loop diuretics becomes necessary.

**Loop diuretics.** Once the GFR falls below 25 mL/min, the loop diuretics become a vital component in the control of extracellular fluid volume and hypertension. The response to loop diuretics is dependent on the delivery of the drug to its site of action (pharmacokinetics) and the initiation of the desired response once the drug reaches the medullary thick ascending limb (pharmacodynamics).<sup>35</sup> Brater and Voelker<sup>35</sup> described a two-step dosage titration process. First, it is necessary to establish a dose that will elicit the desired response. This is best achieved with upward dosage titration. For example, with furosemide, intravenously administered doses of 40, 80, 160, and 320 mg would be given until a response is obtained. A recent study of patients with creatinine clearance values less than 20 mL/min showed that a single intravenous dose of furosemide (160 mg) was sufficient to reach an effective point on the dosage-response curve in all cases. The time course of response as determined by the onset of natriuresis was less intense but more prolonged compared to patients with normal renal function.<sup>36</sup> These intravenous doses are equivalent to 320 to 400 mg of furosemide given orally. For bumetanide, the equivalent oral dose is 4 to 5 mg. Second, the best program to obtain a sustained effect should be determined. The effective dose should be given two or four times a day as needed. Also, the addition of either hydrochlorothiazide (50–100 mg/day) or metolazone (2.5–10 mg/day) to a loop diuretic increases the

likelihood of response.<sup>37</sup> Problems can occur with these larger doses. The risk of toxicity (especially ototoxicity and hyponatremia) increases and at some point the decreased filtered load of sodium renders diuretic use ineffective. It is probably better to initiate alternate treatment than to persist with regimens that contribute to the symptoms of advancing uremia.

**Potassium-sparing agents.** Potassium excretion decreases as the GFR falls, and the risk of hypokalemia with diuretic use is less than in patients with normal renal function. Serum potassium should be monitored and supplements given only if necessary. The potassium-sparing diuretics—alone or in combination with hydrochlorothiazide—are usually not necessary to maintain potassium homeostasis and can cause hyperkalemia with the impaired renal handling of potassium in chronic renal failure. Generally, these drugs should be avoided.

### Second-line agents

The usual hemodynamic abnormality with established renal hypertension is increased total peripheral resistance.<sup>38</sup> As mentioned previously, many pressor mechanisms can contribute to this final common mechanism. Drugs that act against these pressor mechanisms and lower total peripheral resistance can be used as second-line agents. If salt and water retention are not problems, second-line medications may also be used as initial therapy. As mentioned above, preliminary studies show that agents such as ACE inhibitors and calcium channel blockers may play important roles in the prevention of progressive renal failure and may become preferred first-line agents.

**Beta blockers.** Several beta blockers are available in the United States. These agents have been used with good results in patients with chronic renal failure. Their effects include decreased heart rate, cardiac output, mean arterial pressure, central sympathetic discharge, and peripheral norepinephrine release. They also inhibit renin release and thus interfere to a variable degree with the RAA axis.<sup>39</sup>

Total peripheral resistance is acutely increased with most agents but probably returns toward pretreatment values with chronic therapy.<sup>40</sup> The effects of individual beta blockers on renal function are variable. They rarely interfere with renal function to any appreciable degree. They have little or no clinical effect on the GFR, renal plasma flow, renovascular resistance, urinary sodium, or potassium excretion. Although Bauer and Reams<sup>40</sup> have observed decreased renal blood flow with propranolol and increased renal blood flow with nadolol, it is unclear

whether these effects continue on a chronic basis.

An important consideration in the use of beta blockers in chronic renal failure is the relative lipophilicity/hydrophilicity of an individual agent since hydrophilic agents (atenolol, acebutolol, and nadolol) are mostly excreted in the urine, have a longer serum half-life, and require significant dosage adjustment with progressive renal failure.

Most beta blockers raise triglycerides and lower high-density lipoprotein levels. Only the agents with intrinsic sympathomimetic activity, such as acebutolol and pinidolol, do not produce these changes.<sup>1</sup>

Other considerations in the selection of beta blockers are the same as for any patient. The cardioprotective effect of selected beta blockers in patients with coronary artery disease is an additional benefit.

**Blocker dilators.** A new class of agents combining alpha and beta blockade has emerged. These agents cause a greater decrease in total peripheral resistance than is seen with beta blockers. The one available agent, labetalol, does not require dosage adjustment with chronic renal failure,<sup>41</sup> and there are no untoward effects on renal blood flow or GFR. Labetalol also is effective when given intravenously and can be useful in the treatment of hypertensive urgencies or emergencies as either a minibolus administration or via continuous infusion. Labetalol does not appear to adversely affect plasma lipids.<sup>1</sup>

**Alpha blockers.** The two available alpha<sub>1</sub> blockers are prazosin and terazosin. Prazosin has been available for several years; its extensive use is described by Vincent et al.<sup>42</sup> Information on terazosin, a newer agent, is limited, especially on its use in patients with chronic renal failure.<sup>43</sup>

Both agents are peripheral alpha<sub>1</sub> blockers. Little or no dosage adjustment is necessary with chronic renal failure since metabolism occurs in the liver. Neither agent appears to have a deleterious effect on plasma lipids.<sup>42</sup> The GFR and renal blood flow are not significantly affected by prazosin,<sup>44</sup> but an increased sensitivity to prazosin has been reported by Chaignon et al<sup>45</sup> in patients with chronic renal failure. Thus it is prudent to begin with lower doses of either agent. Doses of prazosin in the range of 3 to 8 mg/day have been as effective or more effective than higher doses in patients with chronic renal failure.<sup>46</sup> Terazosin has better bioavailability, a longer half-life, and requires only one dose daily.

**Central agonists.** The available centrally acting agonists include methyldopa and the related drugs—clonidine, guanabenz, and guanfacine. Methyldopa has been available since 1963, and there is extensive clinical

experience with its use in patients with chronic renal failure. Some decrease in the GFR may occur with chronic use of methyl dopa, although the evidence is not clear cut.<sup>44</sup>

A greater concern is the accumulation of active metabolites with worsening renal function.<sup>47</sup> Because of this accumulation, dosage adjustment is necessary. Pseudotolerance may develop with any central agonist secondary to salt and water retention and can be problematic in patients with impaired renal function. Conversely, the antihypertensive potency of these drugs is increased with control of salt and water status.<sup>48</sup>

With any central agent, typical side effects are dry mouth (which may increase fluid intake), drowsiness, orthostatic hypotension, and weakness. There is probably no significant effect on plasma lipids.

Clonidine has no significant effect on GFR or renal blood flow.<sup>49</sup> In addition to a central agonist effect, it interferes with renin and catecholamine activity.<sup>44</sup> However, there is concern regarding rapid withdrawal of clonidine, because a discontinuation syndrome has been recorded, especially with doses above 1.2 mg/day.<sup>50</sup> There are no active metabolites, but the parent compound does accumulate and dosage adjustment is necessary, especially with a GFR below 20 mL/min. There does not appear to be any loss in effectiveness (i.e., a possible "therapeutic window" effect) with higher serum drug levels, as had been suspected.<sup>51</sup>

Guanabenz is a central agonist with a structure similar to clonidine. Less than 1% of the parent drug is excreted in the urine, and no significant accumulation occurs with chronic renal failure. Similar to other central agonist drugs, it is best to begin with low doses and slowly increase the dosage.<sup>52</sup> A withdrawal syndrome may be seen if treatment is suddenly stopped.<sup>50</sup>

Guanfacine is also a clonidine-related drug that undergoes both hepatic and renal metabolism with no significant accumulation in the presence of chronic renal failure.<sup>53</sup> No dosage adjustment is necessary, but small starting doses are prudent. Guanfacine acutely decreases GFR and renal blood flow,<sup>54</sup> although chronic effects are less clear.

**ACE inhibitors.** ACE inhibitors have multiple potential benefits in patients with chronic renal failure. They are well tolerated. As mentioned above, ongoing studies may provide evidence of a specific protective effect for the damaged kidney. Most patients with chronic renal failure have increased plasma renin activity,<sup>24</sup> which is one of several probable targets for these drugs. Results of studies evaluating the effectiveness of ACE inhibition in chronic renal failure differ. Some have

found that only those patients with increased plasma renin activity respond, whereas other studies have shown effectiveness in almost all patients.<sup>24</sup>

Three ACE inhibitors are available. Captopril was synthesized as a specific inhibitor of the enzyme that activates angiotensin II and degrades bradykinin.<sup>55</sup> Giudicelli et al<sup>56</sup> report extensive clinical experience with its use in patients with chronic renal failure. Enalapril is a pro-drug that is transformed in the liver to the active drug enalaprilat.<sup>57</sup> Lisinopril is a lysine analog of enalaprilat that is orally active. Although clinical experience is less extensive with this newer ACE inhibitor, it has been used successfully in patients with chronic renal failure.<sup>58</sup>

All ACE inhibitors are excreted via the kidney. With chronic renal failure, significant delay occurs in peak concentrations and in excretion rates. Consequently, blood levels are increased. Dosage reduction is necessary, especially with the GFR below 50%.<sup>59</sup> As expected, there is no deleterious effect on GFR or renal blood flow.<sup>44,57</sup> Changes in the lipid profile do not occur.

Problems with dysgeusia, leukopenia, rash, and proteinuria are dose-dependent and were reported mostly in early studies using higher doses of (mainly) captopril, as reviewed by Vidt et al.<sup>55</sup> Hyperkalemia can be a significant side effect, especially with worsening renal function. All potassium-sparing agents should be discontinued before initiating therapy with ACE inhibitors. Hypotension can be significant and prolonged, especially with concomitant diuretic use or large starting doses. It is prudent to begin with one-half the usual dose and to discontinue or at least decrease the dose of the diuretic.

If hypertension is related to severe bilateral renal artery stenosis or significant stenosis of a solitary kidney, a deterioration of renal function or acute renal failure can occur. This is especially a problem with associated salt and water depletion.<sup>60</sup> We have also observed rising serum creatinine levels in patients with chronic renal failure treated with ACE inhibitors. This may be an indication of significant loss of renal function and decreased renal reserve so that disruption of intraglomerular adaptive mechanisms with ACE inhibition leads to decreased GFR and increased serum creatinine levels. Whether this phenomenon is detrimental to the damaged kidney is unknown. Clinicians differ in their response to this phenomenon; some continue the medication, but others prefer to switch to another second-line drug.

**Calcium channel blockers.** Three calcium channel blockers are available, although only verapamil is ap-

proved for treatment of high blood pressure. Several newer agents will soon be available. These agents act by interfering with voltage-dependent calcium channels in vascular and cardiac smooth muscle. Calcium channel blockers differ in their relative specificity for cardiac or vascular smooth muscle, although all produce some degree of peripheral vasodilation.<sup>61</sup> Nifedipine is the most potent vasodilator. Newer calcium channel blockers undergoing studies are generally dihydropyridines related to nifedipine in structure. Verapamil, which is related to papaverine, has the greatest effect on cardiac conduction, although it also produces peripheral vasodilation. Diltiazem has a nearly equal effect on both cardiac and vascular smooth muscle.

Calcium channel blockers can influence renal vascular tone and blood flow, hormonal secretion, GFR, and epithelial transport, as recently reviewed by Romero et al.<sup>62</sup> Observed effects of calcium channel blockers on renal function may be present in the acute state but not during chronic administration.<sup>63</sup> Acutely, calcium channel blockers increase renal blood flow with the degree of vasodilation related to the initial resting tone of the vascular smooth muscle. There is also an increase in urinary sodium excretion and plasma renin levels. Long-term studies show no deleterious effect on renal function in patients with hypertension.<sup>62,63</sup> Nifedipine-induced renal dysfunction has been reported possibly secondary to alterations in renal hemodynamics.<sup>64</sup> Although the exact mechanism producing this renal dysfunction was unclear, it seemed to occur only in a small subset of elderly patients with atherosclerotic disease and chronic renal failure and was reversible with discontinuation of the drug. At least in the remnant model of chronic renal failure, verapamil has also been shown to be protective against progression of renal damage.<sup>65</sup>

Additional benefits with these agents include a cardioprotective effect in patients with atherosclerotic heart disease, no adverse changes in the lipid profile, and a prophylactic role in patients with vascular headaches. Dose adjustment is not required with chronic renal failure. In patients taking phosphate binders, particularly aluminum hydroxide-containing antacids, the tendency for verapamil and diltiazem to cause constipation can be especially problematic.

**Vasodilators.** Although several of the aforementioned medications can be considered vasodilators, as they decrease peripheral vascular resistance, hydralazine and minoxidil will be considered here. Both are third-line drugs. Neither significantly affects GFR, although both increase renal blood flow.<sup>44</sup> Concomitant use of a sympatholytic agent to blunt reflex tachycardia and a di-

uretic to prevent salt and water accumulation is required. Hydralazine undergoes acetylation in the liver and has a longer duration of action in patients with renal failure because of active metabolites that are excreted through the kidneys.<sup>66</sup> It has the advantage of being active by oral, intramuscular, or intravenous administration and can be used for acute treatment of worsening hypertension. Response, however, is less predictable than with other available agents and its use in treatment of hypertensive urgencies and emergencies has declined.

Historically, the use of minoxidil made bilateral nephrectomy unnecessary in the vast majority of patients with chronic renal failure and uncontrolled hypertension.<sup>67</sup> It is metabolized in the liver with only about 10% to 12% excreted unchanged in the urine. There is no significant dosage adjustment with renal failure. It is unclear if the risks for pericardial effusion are increased in patients with chronic renal failure.<sup>68</sup> Hirsutism is to be expected and can limit the acceptance of this medication, particularly in children and women.

### Hypertensive urgencies and emergencies

The full consideration of hypertensive emergencies is beyond the scope of this article, and has been reviewed recently.<sup>69,70</sup> The main consideration with severely increased blood pressure is whether it represents a hypertensive emergency wherein blood pressure must be lowered within an hour to reduce ongoing vital organ damage. Hypertensive emergencies require hospitalization and parenteral medication. A hypertensive urgency is a situation in which blood pressure elevation is not causing immediate end-organ damage but should be controlled within 24 hours to reduce potential risks. Urgencies may be treated with oral agents and may or may not require hospitalization.

**Oral agents.** Several of the previously discussed medications have been used effectively in hypertensive urgencies and emergencies in patients with chronic renal failure. Since salt and water accumulation is a frequent concomitant problem, diuretics, particularly loop diuretics, are important in almost all situations. Drugs that have been effective when given orally include clonidine, captopril, and nifedipine.<sup>70</sup> The latter two agents lower blood pressure in most patients within 30 to 60 minutes and may keep blood pressure under control for up to four to six hours. Clonidine (0.2 mg given initially and 0.1 mg given each hour) usually lowers blood pressure in two to three hours.<sup>70</sup> Traditional vasodilators such as hydralazine and minoxidil have also been used, with the caution that both a diuretic and a sympatholytic agent must be given at the same time. Of course, with any oral

agent, the decline in blood pressure will persist as long as the drug is present, and hypotension, if it develops, can be a problem.

**Parenteral agents.** Again, salt and water accumulation frequently occurs in hypertensive emergencies, and intravenous loop diuretics are an integral part of parenteral treatment.

Diazoxide is a direct-acting arterial dilator with a rapid onset of action. There is decreased protein binding with chronic renal failure and a potentially greater risk of overshoot or prolonged hypotension.<sup>71</sup> Because of this concern, two alternative methods of delivery have been used.<sup>69</sup> A minibolus injection (50 to 100 mg at 10- to 15-min intervals) or slow continuous infusion (approximately 10–30 mg/min) has produced a more controlled reduction in blood pressure. Use of diazoxide in situations including acute cerebral and coronary insufficiency requires caution. Reflux tachycardia and increased myocardial oxygen consumption can occur with coronary insufficiency.

When cerebral autoregulation is lost as in intracranial hemorrhage or cerebral infarction, use of short-acting agents is required to prevent aggravation of existing deficits secondary to a prolonged decrease in cerebral perfusion. Nitroprusside offers the advantages of potent, minute-to-minute, predictable reduction in blood pressure regardless of etiology. As with all parenteral agents, close continuous monitoring of blood pressure is required to prevent overshoot hypotension. Because nitroprusside is converted in vivo to thiocyanate, which accumulates in renal failure, toxicity can be a problem. In general, use should be limited to less than 48 hours.<sup>69</sup> Thiocyanate toxicity is usually manifested as neurologic abnormalities, including hyper-reflexia, confusion, and seizures. However, these clinical manifestations are inconsistently observed, and monitoring of thiocyanate blood levels is mandatory to avoid blood levels above 10 mg/dL.<sup>72</sup> Acute accumulation of cyanide and resultant metabolic acidosis can also occur, especially in patients with underlying liver abnormalities.

Labetalol, a combined alpha and beta blocker, pro-

duces prompt reduction in blood pressure and systemic vascular resistance without reflex tachycardia or change in cardiac output.<sup>73</sup> An additional advantage is that no dosage adjustment is required with chronic renal failure, as labetalol is hepatically metabolized. Any contraindication to the use of a beta-blocking agent also exists with this drug. The use of more frequent and smaller boluses (20 to 40 mg) by intravenous push every 15 minutes or intravenous infusion of 0.5–2.0 mg/min has been shown to be as effective as larger boluses and to decrease the risk of prolonged hypotension.<sup>69</sup>

## CONCLUSION

It is often unclear in patients with renal insufficiency and hypertension whether the kidney is the culprit or victim. Regardless, there are several important reasons why strict control of blood pressure is mandatory for these patients. Treatment and control of hypertension is probably the most important factor in preventing progression of underlying renal insufficiency. In addition, uncontrolled hypertension is an important risk factor for atherosclerosis, which remains the most common cause of death in patients with chronic renal failure. Ongoing trials involving patients with chronic renal failure should further clarify the extent of blood pressure control necessary.

Despite continued controversy about the initial pathophysiologic events in the initiation of hypertension, the primary hemodynamic derangement in fixed hypertension is increased peripheral vascular resistance. The use of diuretics, particularly loop diuretics and agents that decrease peripheral vascular resistance, are the mainstays of treatment. Attention to pharmacokinetic data for antihypertensive agents used is particularly important. Both the effectiveness and the side-effect profile of an agent can vary with changing renal function. It is necessary to continually re-evaluate the degree of blood pressure control, the underlying renal function, and the progression of any associated medical problems.

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