SUMMARY

Hypertension that is truly resistant to modern antihypertensive therapy is uncommon. In the majority of cases, apparent resistance is more likely associated with poor patient adherence, interacting drugs, drug interactions, and inappropriate drug dosages. Sodium and fluid volume play a major role in resistant hypertension. There is considerable evidence to support the role of dietary sodium restriction in successful nonpharmacological treatment of hypertension. Salt sensitivity in humans appears to represent at least one factor determining individual susceptibility to variable salt intakes. Sodium and water retention may lead to refractoriness to many antihypertensive agents, and there is evidence to suggest that extracellular fluid volume expansion also plays a role in many hypertensive patients. While retention of sodium and water is well established early in patients with renal parenchymal disease, hypertension associated with progression of renal parenchymal disease is complicated by other factors that include interactions between hemodynamic and humoral factors, functional changes in adrenergic responses, and structural vascular disease. The role of other cations such as potassium, calcium, and magnesium in resistant hypertension has yet to be established. (Hypertension 11 [Suppl II]: II-76-II-83, 1988)

KEY WORDS

renal failure

THE definition of resistant hypertension and a working classification for the patient that is refractory to appropriate therapy have been covered in other reviews in this monograph. This review will concentrate primarily on the role of sodium and fluid volume and on the role of the kidney in resistant hypertension.

All patients with hypertension who are unresponsive to pharmacological therapy should not be considered as having truly resistant hypertension. Failure to control even moderate to severe hypertension with medication in clinical practice is most commonly associated with poor patient adherence to the prescribed drug regimen. Other factors that have been considered include the use of interacting drugs (which raise blood pressure), competing drug interactions, and inappropriate dosages or combinations of available drugs.

Role of Sodium

A correlation between sodium intake and the prevalence of hypertension has been demonstrated in a number of industrialized and nonindustrialized societal groups (Figure 1). Blood pressure rises with age in those societies where sodium is added to food in comparison with those societies where sodium intake remains low.1,2 Considerable evidence supports dietary sodium restriction as an important element in the successful nonpharmacological treatment of many patients with essential hypertension. The average daily intake of salt in the United States approximates 10 to 13 g/day (Na 170-225 mEq/day). Excessive sodium intake in treated hypertensive patients or failure to restrict sodium to a suitable degree has long been considered a major problem in hypertension management. Excessive sodium intake may negate the reduction in extracellular sodium and fluid volume associated with diuretic therapy and may significantly impair the effects of other antihypertensive drugs.

Early studies clearly demonstrated that severe sodium restriction will invariably lower blood pressure. Significant reductions in blood pressure were seen in 60 to 70% of hypertensive patients subjected to diets containing Na 9 to 15 mEq/day.3-5 In the 1940s, Kempner6 reported the reduction of blood pressure in more than 65% of 500 patients subjected to a rice-fruit-water diet containing Na 10 mEq/day. His observations included patients with accelerated or malignant hypertension. Unfortunately, diets restricting sodium to this degree were not suitable for long-term therapy because of unpalatability and poor patient compliance.
for even short periods of such aggressive dietary sodium restriction.

Recent reports have cited the benefits of moderate sodium restriction as primary therapy in selected patients with mild hypertension and as an important adjunct to pharmacological regimens in patients with moderate to severe hypertension. While sodium restriction may not achieve the same degree of reduction of blood pressure as diuretics, it has proved an important adjunct to diuretics, with the combination being superior to either therapy used alone. While earlier studies on moderate sodium restriction were generally poorly controlled, overall observations did demonstrate that the higher the blood pressure, the greater the effect of sodium restriction. This relationship has been seen regardless of the degree of sodium restriction or the duration of restriction. More recent studies have been better controlled and have extended earlier observations. MacGregor et al. studied a group of 19 patients initially placed on a diet containing Na 60 to 100 mmol/day and then randomly assigned, in a crossover study, to take either sodium chloride capsules, returning sodium intake to prestudy levels, or identical-appearing placebo capsules. While blood pressure returned almost to prestudy levels when sodium chloride was added, pressures remained the same during the low sodium period. In a recent study, MacGregor et al. tested the hypothesis that the reduction in blood pressure on a sodium-restricted diet is related to pretreatment levels. In 103 normotensive and hypertensive subjects, observations were reported during a normal sodium diet (115 mmol/day), after a high salt diet (350 mmol/day), and following ingestion of a low sodium diet (10 mmol/day). The fall in blood pressure that occurred when changing from the normal or high sodium diet to a low sodium diet was seen to correlate with the pretreatment level of blood pressure. Beard et al. randomly assigned 90 hypertensive patients, all of whom remained on antihypertensive drug therapy, to a sodium-restricted diet (37 mmol/day) or to a normal sodium intake (161 mmol/day). Patients on the sodium-restricted diet had a greater fall in blood pressure that enabled a significant reduction in antihypertensive medication during the trial, whereas the control group demonstrated a smaller reduction in blood pressure and required full amounts of medication. In all of the studies reported, there was ample evidence to suggest that all hypertensive patients are not responsive to alterations in sodium intake.

Selective inbreeding of rats has produced strains highly susceptible or resistant to sodium. Cross-transplantation studies have demonstrated that the genetic defect is manifested in the kidneys. Tobian has shown in isolated rat kidneys that salt-sensitive kidneys excreted less sodium than the salt-resistant kidneys. Essential hypertension in humans also appears to have an important genetic component, which may be associated with defective renal sodium excretion. Luft et al. have shown that blacks, older subjects, and first-degree relatives of patients with essential hypertension all failed to excrete a sodium load at the same rate as control subjects. Blacks and older subjects also had lower renin values. These observations suggest that the intrinsic renal abnormality in blacks and older subjects resulted in subtle fluid volume expansion. There is now evidence to suggest that a circulating inhibitor of sodium pumps in the kidney and other cells, including vascular smooth muscle, plays a role.
in essential hypertension.\textsuperscript{17, 18} Rather than distinct salt-sensitive or -resistant responsiveness, it is more likely that human populations represent a continuum of responsiveness with greater responses seen in older patients, in those with higher blood pressures, and in those who have a smaller rise in renin-aldosterone levels. These factors, taken together, may determine individual susceptibility to variable sodium intakes.

The mechanisms by which changes in the sodium intake influence blood pressure remain controversial. Studies have suggested that blunted responsiveness of the renin-angiotensin system contributes to the blood pressure lowering effect of sodium restriction.\textsuperscript{19, 20}

The sympathetic nervous system may help determine the antihypertensive effect of a sodium-restricted diet, possibly by interference with release of neurotransmitters, with neuronal uptake, or with storage of norepinephrine in the vesicles.\textsuperscript{21, 22} Recent observations suggest that the fall in blood pressure with sodium restriction is, at least in part, mediated by decreased end-organ responsiveness to adrenergic stimulation.\textsuperscript{23} Whether the reduced vascular reactivity at the end of low sodium treatment is due to down regulation of the adrenergic receptors is not determined. In contrast, experimental studies in spontaneously hypertensive rats suggest a linear correlation between vascular reactivity and sodium intake, with increased reactivity observed with sodium loading. These changes could not be attributed to fluid volume expansion. Inactivation of norepinephrine by neuronal uptake was impaired by a high sodium intake.\textsuperscript{24} Similar changes have been observed in humans.\textsuperscript{25}

**Role of Fluid Volume**

It is not possible to separate fluid volume from sodium as factors in the generation of hypertension. In animals, increases or decreases in extracellular salt with volume held constant has no immediate effect on blood pressure.\textsuperscript{26, 27} In hypertensive humans, an increase in plasma volume without an increase in salt, by use of isotonic dextran infusions, did not alter antihypertensive responses.\textsuperscript{28}

The chronic administration of many antihypertensive agents is associated with sodium and water retention and may lead to refractoriness of the treatment. Early reports by Finnerty and colleagues\textsuperscript{29} and Davidov and associates\textsuperscript{30} emphasized the sodium and volume retaining properties of diazoxide and clonidine. Prolonged administration of both agents was frequently accompanied by weight gain and by blood pressure that was refractory to even maximal doses of these medications. The addition of a diuretic to the regimen was followed by weight loss in some and a decrease in blood pressure and suggested that an expanded extracellular fluid (ECF) volume contributed to the drug resistance. To test this hypothesis, Finnerty\textsuperscript{31} evaluated changes in ECF volume and blood pressure in 14 patients receiving drug therapy without diuretics. Four patients received intravenous diazoxide, while 10 received methyldopa or hydralazine orally. A rise in weight, ECF volume, and blood pressure was noted during the period of monotherapy. The addition of furosemide or chlorothiazide in these patients (none of whom was uremic) was followed by a reduction in weight and ECF volume and improved blood pressure control. Observations were extended to 73 patients with refractory hypertension on multiple drug regimens, including thiazide diuretics; many of these patients had impaired renal function. The addition of furosemide to the regimen (average 240 mg) lowered blood pressure and improved responsiveness to antihypertensive drugs.\textsuperscript{28, 32} In 89% of the 73 patients with refractory hypertension on multiple drugs, blood pressure control was maintained with lower doses of previously administered agents. Dustan et al.\textsuperscript{33} studied the relationship between arterial pressure and plasma volume in 16 hypertensive patients treated with adrenergic blocking drugs, alone or in combination with a thiazide diuretic. In five with severe essential hypertension, blood pressure control had been poor despite combined therapy with adrenergic blockers and a diuretic; plasma volume was expanded or normal. Intensified diuretic treatment reduced plasma volume below normal and arterial pressure to nearly normal. Figures 2 and 3 show the correlation of systolic and diastolic blood pressures and plasma volume in 12 male patients. In 11 patients who had responded well to treatment with combination therapy or adrenergic blockers alone, plasma volume was below normal. The results suggested that treatment with adrenergic blocking drugs so modifies cardiovascular control that blood pressure becomes directly related to intravascular volume; this further emphasizes the importance of volume control during hypertension therapy.

These observations should not suggest that ECF volume is expanded in all patients with hypertension. To the contrary, measured ECF and plasma volumes are normal in most hypertensive patients. Freis\textsuperscript{34} reminds

\begin{figure}[h]
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\caption{The relation of systolic arterial pressure and plasma volume, expressed in percentage of normal, in 12 hypertensive men treated with adrenergic blocking drugs or diuretics. Closed circles represent values from all patients, and open circles indicate the first values obtained in four of these 12 when both pressure and volume were inadequately controlled and before diuretic treatment was intensified. (Reprinted from Dustan et al.\textsuperscript{33} with permission.)}
\end{figure}
us that this observation is not inconsistent with a volume-sodium load hypothesis because the kidney maintains ECF homeostasis by virtue of an elevated blood pressure. It may well be that the ECF volume is expanded by standards of unacculturated populations. Hypertensive patients consuming a Kempner rice diet with Na < 10 mEq/day have demonstrated an approximate 15% reduction of ECF volume. In addition, unacculturated populations exhibit characteristics usually associated with ECF volume depletion, including increased plasma renin activity and aldosterone excretion despite low normal levels of blood pressure. Guyton has concluded that the common denominator in the development of any chronic elevation in blood pressure is the need for the kidney to increase both volume and sodium excretion to prevent a chronically expanded ECF volume. A genetic defect in the handling of sodium by the kidney in essential hypertension would result in a higher perfusion pressure to maintain ECF homeostasis in the presence of a high sodium intake.

Role of Potassium

Population studies have demonstrated that those population groups with low salt intake also have a high potassium intake. Sasaki and colleagues have reported observations on two villages in northern Japan where salt intake was similar but blood pressure differed. In the village where blood pressure was lower, much higher potassium intake was observed. Several other studies have reported a negative correlation between potassium excretion and blood pressure. It has been shown that blacks excrete less potassium than white patients and that differences in blood pressure between blacks and whites are accompanied by differences in potassium excretion. Experimental and clinical data are available to show that potassium depletion can lower blood pressure in humans with hypertension. Conversely, a high potassium intake can also lower blood pressure in those with hypertension. A modest reduction in blood pressure of 3 to 10% has also been observed with potassium intakes of 120 to 175 mEq/day. There is no evidence that would suggest a causative role for potassium in refractory hypertension. It seems premature to recommend a high potassium diet indiscriminately at this time, but the encouragement of well-controlled studies to assess the benefits associated with potassium supplementation would appear appropriate. The potential therapeutic benefit of a low potassium intake is even less clear at this time.

Role of Calcium and Magnesium

Several studies suggest that reduced intake of calcium or magnesium is associated with an increased risk of hypertension. While information about magnesium is very limited, it is recognized that both cations are involved in vascular tissue processes important to the physiological regulation of blood pressure. Recent evidence has suggested that oral calcium supplements can lower blood pressure. Magnesium has long been used to treat severe hypertension and encephalopathy associated with eclampsia, and one study has reported lowering blood pressure with chronic oral supplementation. Comparable intake data are not available for magnesium, but one report has shown similar magnesium intake among normotensive and hypertensive women.

There are no data currently available regarding deficient dietary intake of these cations in the patient with refractory hypertension. However, it is possible that calcium and magnesium balance could be important in the efficacy of certain antihypertensive agents. Further well-controlled investigations are needed to assess the role of adequate ingestion of potassium, calcium, and magnesium in the dietary management of hypertension.

Role of the Kidney

Hypertension develops in most patients with chronic renal parenchymal disease and often does so months or years before renal function has deteriorated to the point where dialysis or transplantation becomes necessary. In renal parenchymal diseases with involvement of small vessels and glomeruli, hypertension occurs early in the disease, even when renal function is minimally impaired, and persists until end-stage disease is apparent. Conversely, among interstitial diseases, hypertension is often absent early, but as renal function deteriorates, the prevalence of hypertension approaches 100% regardless of the type of disease present. While there is ample evidence to suggest that multiple factors are involved in the pathophysiology of renal parenchymal hypertension, volume expansion appears to be the causal or a major contributing factor in most patients. Blood volume and total body sodium are increased with moderate renal insufficiency. However, it is possible that calcium or magnesium is associated with an increased risk of hypertension.
processes return blood flow toward normal but at the expense of an increased peripheral vascular resistance.

Alterations in cardiac output have been demonstrated very early in renal parenchymal disease. Broedel made several hemodynamic measurements in patients with early renal parenchymal disease. Twelve initially normotensive patients had an increase in blood volume and cardiac output with a simultaneous decrease in peripheral resistance. Hypertension subsequently developed in 11, and those with mild to moderate hypertension had increased cardiac output with normal peripheral vascular resistance. Those with more severe hypertension all had an increase in peripheral resistance. The association of a high cardiac output with early hypertension of renal parenchymal disease has been confirmed by Onesti et al. who assessed hemodynamic parameters in patients on dialysis. They found that the increased output was due to anemia. When the anemia was corrected, cardiac output decreased, peripheral resistance rose and was associated with a marked increase in blood pressure. Thus, a high cardiac output occurs early in the course of renal parenchymal hypertension, followed by a rise in peripheral vascular resistance as the disease process and renal failure progress.

Neurogenic factors play a part in the modulation of cardiac output changes in response to altered blood volume. In essential hypertension, increased renal vascular resistance can be reduced by phentolamine or splanchic blockade. In renal parenchymal disease, the increase in renal vascular resistance is more fixed and less responsive to vasodilating compounds. Evidence suggests that some patients with chronic renal failure have significant autonomic insufficiency, probably associated with generalized neuropathy, which may contribute to the pathogenesis of hemodialysis-induced hypertension. Significant autonomic dysfunctions may limit tolerance to dialysis ultrafiltration and is associated with higher supine blood pressure, both predialysis and postdialysis. Stimulation of both plasma renin activity and norepinephrine by dialysis-induced hypertension is consistent with activation of baroreceptor reflexes leading to secondary renin release. Tector et al. showed a failure of postdialysis hypertension to stimulate either plasma renin activity or norepinephrine in some patients with renal failure. These results suggest that lack of norepinephrine or renin responsiveness may be another measure of abnormal autonomic function in uremia.

The presence of both vasoconstrictor and vasodilator compounds within the kidney leads, of course, to considerable interest in their potential role in renal parenchymal hypertension. Numerous studies have shown significant increases in plasma angiotensin II levels that correlate with levels of diastolic blood pressure. An early study by Vertes et al. demonstrated two patterns of response to achievement of "dry weight" by hemodialysis. In 35 of 40 patients, there was an excellent response to ultrafiltration dialysis. In five patients, blood pressure was not controlled despite aggressive ultrafiltration to dry weight, and these patients remained refractory to antihypertensive drugs. In this small subgroup, plasma renin activity was 10-fold higher than in the volume-responsive group. These observations led to the concept of volume-dependent or renin-dependent hypertension in patients with renal failure. In patients with high plasma renin activity, increased peripheral resistance, and normal or decreased cardiac output, bilateral nephrectomy reduced plasma renin activity, blood pressure, and peripheral resistance to normal, suggesting an etiologic role for the renin-angiotensin system in at least some patients. The converting enzyme inhibitor captopril has been shown to control blood pressure in patients with severe, refractory hypertension of renal origin. Ramos achieved rapid initial control of blood pressure in 69 of 89 patients with drug-resistant malignant hypertension by administration of captopril in doses of 50 to 150 mg. In a subgroup of 11 patients, eight responded with significant reductions in mean arterial pressure. The fall in total peripheral resistance correlated highly with the prevailing levels of plasma renin activity. Brunner et al. successfully used captopril to treat seven patients who had refractory hypertension associated with chronic renal failure. None of the patients had high plasma renin activity. These findings suggest that renin levels may not reflect the role of the renin-angiotensin system and, although normal or low, may still be inappropriate in relation to subtle degrees of sodium and volume retention.

Captopril has also been effective in controlling severe, refractory hypertension of renal origin, including inpatients with hypertension following renal transplantation. Converting enzyme inhibition may also facilitate sodium excretion by the kidneys and potentiate the natriuretic effect of diuretics.

In a study of seven anephric patients, Veld et al. administered captopril to seven patients who were fluid-depleted following dialysis and again after fluid repletion. Orthostatic hypotension developed in all patients after captopril administration in the fluid-depleted state. In the fluid-replete state, 2 days after hemodialysis, captopril had no effect on blood pressure. The plasma concentration of active renin was extremely low and did not rise after fluid withdrawal or captopril administration. Thus, the hypotensive effect of captopril did not appear to depend on the circulating renin concentrations in these patients. Possible effects of captopril on angiotensin II in blood vessel walls or possible effects on preload reduction were postulated to explain the orthostatic hypotension in these anephric patients when they were fluid-depleted; this further complicates the tendency to categorize these patients as volume dependent or renin dependent. B-Adrenergic blockers may be effective in the control of refractory hypertension with renal failure, including patients on dialysis. Propranolol results in decreased blood pressure and suppression of elevated plasma renin levels. Propranolol may be effective, particularly in higher doses, despite low or normal plasma renin activity. Different B-blockers have variable effects upon plasma renin activity, and a clinical correlation be-
tween effects on renin and lowering of blood pressure is not consistent. It is possible that other effects of propranolol, that is, a central depressor effect, alteration of sensitivity to angiotensin II, or decreased cardiac output, may play a role in the response. Other lipophilic β-blockers or the newer blocker-dilator agents, such as labetalol, have demonstrated similar effects. While not as potent as minoxidil, labetalol can be an effective substitute for a β-blocker plus hydralazine therapy or can be added to the regimen.59,60

The centrally acting agent clonidine is also effective in patients with renal disease.61 The drug was particularly effective in patients with high plasma renin activity possibly because the plasma renin reflects a higher level of sympathetic drive.

Severe hypertension in patients receiving dialysis who fail to respond to reduction in ECF volume may also be controlled with the addition of the potent vasodilating agent minoxidil. Pettinger and Mitchel62 suggested that minoxidil provided an alternative to bilateral nephrectomy in severely hypertensive patients with renal failure. Volume control in minoxidil-treated patients is difficult and requires concomitant administration of a potent loop diuretic in nondialysis patients, despite aggressive sodium restriction. In patients with end-stage renal disease, ultrafiltration dialysis can be used to maintain a dry weight status. The frequency of tachycardia and risk of anginal symptoms is minimized by adequate β-blockade. Excessive hair growth may limit the use of this agent in women. Control of blood pressure in patients with refractory hypertension of renal origin may be associated with at least initial further deterioration in renal function regardless of the agent or combination of agents used. The calcium channel blockers, particularly nifedipine, have also been effective in the management of refractory hypertension when added to the regimen.63,64 The calcium blockers as a class of agents have several potential advantages in that they do not evoke tolerance in long-term treatment, do not consistently increase plasma renin activity, and appear to induce little or no sodium retention. In selected patients, continued control of blood pressure may be associated with late improvement and stabilization of renal function. Thus, regardless of etiology, renal failure complicating severe hypertension should not be considered a contraindication to aggressive treatment of the hypertension.

The role of renal prostaglandins, kallikrein, and renomedullary depressor lipids in renal parenchymal hypertension has not been clarified. Deficient renal production of these vasodilator and natriuretic substances might contribute to the development of hypertension. Reduced urinary kallikrein excretion has been demonstrated in white but not in black patients with renal parenchymal hypertension.65 Urinary prostaglandin E2 excretion is normal in hypertensive patients with chronic renal parenchymal disease.66 While a deficit in the renal production of prostaglandins may not play a primary role in the hypertension of renal parenchymal disease, it has been demonstrated that glomerular filtration rate and urinary excretion of sodium are impaired when prostaglandin synthesis is blocked. These results suggest a protective role of renal prostaglandin E2, in renal function when hypertension appears in the course of chronic parenchymal disease. The role of these agents in the generation of hypertension in renal parenchymal disease needs further clarification. Similarly, while plasma vasopressin may be elevated in malignant hypertension, there is no conclusive evidence that vasopressin plays a role in clinical hypertension.67

Finally, renal hypertension as a consequence of hemodynamically significant renal artery stenosis must be considered as a cause of refractory hypertension. Estimates of the prevalence of renovascular hypertension vary widely. When considered in the context of the hypertensive population, renovascular hypertension would appear to account for a variable fraction of these patients, ranging from 0.2 to almost 10%. However, when only patients with severe or refractory hypertension are studied, the prevalence is much higher. Davis et al.68 reported that 32% of 76 white patients and 4% of 47 black patients with grade III or IV hypertensive retinopathy had renovascular hypertension.

Reduced renal perfusion in the presence of hemodynamically significant renal artery stenosis causes release of renin and increases angiotensin II levels with resulting vasoconstriction and systemic hypertension. Stimulation of aldosterone by angiotensin II results in water and sodium accumulation with increases in extracellular fluid volume, which helps sustain blood pressure and leads to secondary suppression of angiotensin II. The effects of aldosterone and induced changes in intrarenal hemodynamics are important in the transition from acute phase to the chronic phase of renovascular hypertension; this probably results from activation of multiple pressor mechanisms, described earlier, that sustain the hypertension.

The early pharmacotherapy of renovascular hypertension was empiric and similar to treatment of essential hypertension. Nevertheless, blood pressure control was possible in many patients; the medical treatment of renovascular hypertension has been vastly improved with the development of β-adrenergic blocking agents and the converting enzyme inhibitors because of their potential for blocking the renin-angiotensin-aldosterone system. Despite the availability of these newer agents, pharmacotherapy of some patients with renovascular hypertension may prove difficult. This is particularly true in some patients with moderate to severe hypertension; captopril is not without risk in patients with bilateral renal artery stenosis, a solitary functioning kidney, and azotemia.69,70 In these patients, reduced perfusion and intrarenal effects of captopril (and enalapril) may lead to sudden, severe reduction in renal function. Control of blood pressure and preservation of renal function in such patients may depend upon appropriate interventional therapy, such as surgical revascularization or percutaneous transluminal renal angioplasty.

Aldigier et al.71 have demonstrated that captopril decreases blood pressure and suppresses the renin-an-
giotensin system to the same degree in both essential and renovascular hypertension. Urine sodium excretion was higher in treated essential hypertension than in treated renovascular hypertension, while plasma volume remained unchanged in those with essential hypertension but increased in those with renovascular hypertension. Plasma creatinine was elevated to a greater degree in renovascular hypertension, suggesting the need for caution in the use of converting enzyme inhibitors in patients with renovascular hypertension.

In summary, it is not possible to separate the role of fluid volume and salt in the generation of hypertension, and both factors play a role in refractory hypertension. Retention of salt and water is also well established as an early occurrence in patients with renal parenchymal disease. With progression of disease, it is apparent that complex interactions between hemodynamic and humoral factors, as well as functional changes in adrenergic responses, may contribute to both the hypertension and response to therapy. The role of other cations in resistant hypertension has yet to be established.

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