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In this issue of Current Concepts in Hypertension investigators from the University of Pennsylvania Medical School address several issues of timely importance regarding the kidney and hypertension. Dr. Townsend discusses the increasing prevalence of renal insufficiency and end-stage renal disease among the American hypertensive population. Dr. Cirigliano addresses the increasing challenge of renal vascular hypertension and reviews the results of medical therapy and Drs. Townsend and Malhotra examine the relationship between specific antihypertensive therapy and renal function. Several on-going trials will bring new information on each of these issues in the near future.

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Introduction

Randomized controlled trials of the last 40 years have shown a significant benefit in protecting the heart and brain by treating hypertension with drug therapy.[1,2] Because less is known about the benefit of antihypertensive therapy to prevent the development of chronic renal insufficiency (CRI) and the progression of CRI to end stage renal disease (ESRD) in nondiabetic patients, this issue of the newsletter is devoted to a review of the epidemiology of CRI and the role of hypertension as a risk factor for this progression. In addition, we also review hypertension associated with parenchymal renal disease and with renovascular disease, commenting particularly on medical management of these disorders.

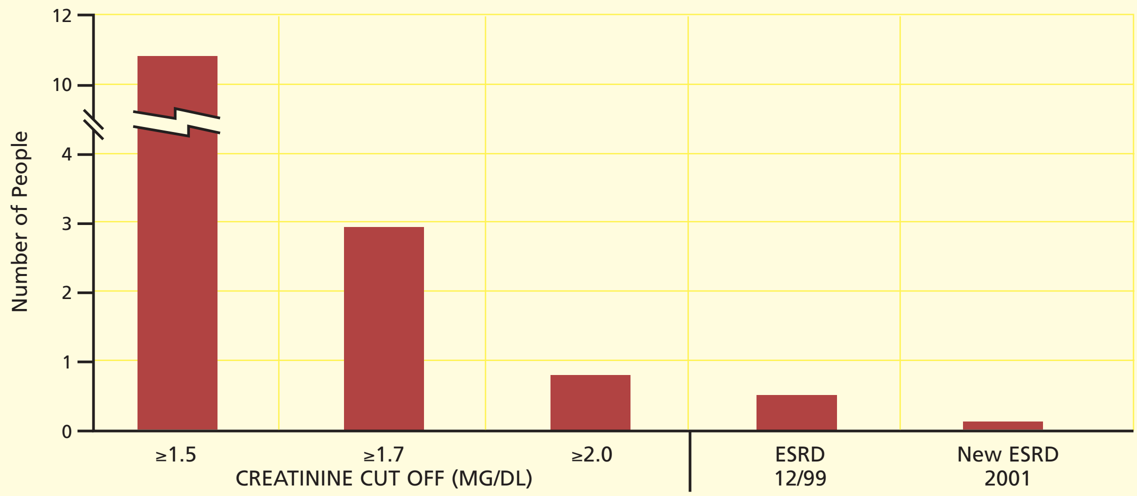
Epidemiology of CRI in the US

The National Health And Nutrition Examination Survey (NHANES III) recently performed serum creatinine determinations as part of the overall evaluation of subjects 12 years of age and older in the US. In this study, 18,723 persons examined between 1988 and 1994 had serum creatinine determinations performed as part of their evaluation. The number of subjects with creatinine values above levels of 1.5 mg/dL, 1.7 mg/dL, and 2 mg/dL is shown in Figure 1, with an extrapolation to the entire US population based on 1990 US Census data. Merged into this figure, on the right side, are data from the United States Renal Data Systems (USRDS) showing the number of patients on dialysis (combined hemodialysis and peritoneal dialysis) and those with a functioning kidney transplant. Subset analyses of this data showed that, overall, men have higher creatinine values than women (1.16 and 0.96 mg/dL, respectively), and that non-Hispanic blacks had higher creatinine values compared with non-Hispanic whites or Mexican Americans. This latter finding is reflected in the USRDS data showing a disproportionate black representation in the ESRD population testifying to the greater vulnerability of the African American kidney to damage from risk factors such as hypertension.

Role of Hypertension as Risk Factor in CRI and ESRD

In Perera's original study of essential hypertension, renal involvement during the course of hypertension was noted frequently.[3] In that study 42% of the patients developed proteinuria, 18% developed azotemia, and 10% died from uremia or its complications in the era before drug therapy. Two more recent clinical trials elucidate further the incidence of CRI and ESRD and the role of CRI as a risk factor for cardiovascular mortality. In the large cohort screened for the Multiple Risk Factor Intervention Trial (MRFIT), the risk of developing ESRD an average of 16 years after the initial blood pressure measurements was strongly and independently correlated to the systolic and diastolic blood pressure at the time of screening.[4] In the Hypertension Detection and Follow-up Program (HDFP), an elevated creatinine (>1.7 mg/dL) at baseline predicted a doubling of 8-year cardiovascular mortality after adjustment for other risk factors.[5]

Figure 1 Prevalence of Renal Insufficiency at 3 Levels of Serum Creatinine Based on the NHANES III Data Extrapolated to the Entire American Population with Estimates of ESRD



Treatment of Hypertension and CRI Progression

Ethnicity modifies the effect of hypertension therapy on renal function. In the MRFIT trial mentioned earlier, blood pressure control was not as effective at preventing an increase in serum creatinine in black as in white men.[6] Recent data clearly show the benefit of blood pressure reduction on kidney function in diabetes. In nondiabetic forms of CRI, several recent trials have provided some hope for slowing the rate of renal function loss and delaying the time to ESRD. The Modification of Diet and Renal Disease study established that more stringent blood pressure control reduced the rate of renal disease progression, particularly when proteinuria is present.[7] The particular benefits of angiotensin-converting enzyme (ACE) inhibitor therapy (in addition to their antihypertensive effects) in preserving renal function have been promoted in recent clinical trials.[8,9] The African American Study of Kidney Disease and Hypertension (AASK) trial (in progress) should provide further information on the issue of optimal blood pressure and the choice of drug therapy in African Americans who appear to be the group at greatest risk (and therefore with the greatest benefit) from the consequences of hypertension on renal function.[10]

Summary

Hypertension is an important risk factor for the development of CRI and ESRD. The damage to the kidney in hypertension is likely mediated by the physical effects of the pressure itself on the renal blood vessels, the ultimate balance in the stimulation of adaptive and maladaptive humoral factors resulting from the effects of the pressure, and the degree to which the physical and humoral effects of hypertension are modified by the genetic background and presence and severity of other risk factors in each individual. Presumably, the large Longitudinal Cohort Study of Chronic Renal Insufficiency proposed by NIDDK this year will elucidate further the separate roles of hypertension, genetics, and humoral factors in the progression of CRI and the development of ESRD.

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MEDICAL MANAGEMENT OF RENOVASCULAR DISEASE IN HYPERTENSIVES

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With the recognition of the role of reduced renal blood flow as a mechanism causing hypertension by Goldblatt,[1] reconstructive renal surgery soon followed in an effort to cure hypertension in patients thought to have renovascular hypertension. More recently, renal vessel angioplasty became available (in the late 1970s), followed closely by a rapid growth in literature on the merits of this less invasive means to restore renal blood flow coupled with an almost unquestioning acceptance of its utility in treating renovascular disease. Despite the established role of surgery[2] and the substantial popularity of renal angioplasty, there were few head-to-head randomized comparisons of the two approaches and, until 1998, almost no data on the merits of medical therapy when compared directly to surgical reconstruction or angioplasty (with or without stent placement).

The last decade witnessed several improvements in medical care that prompt a return to the issue of the superiority of a reconstructive approach to renovascular disease compared with conservative medical treatment. Several things, in particular, are worthy of mention in this regard including:

1) an increased recognition of lipid factors in renal disease with
2) greater availability and usage of cholesterol lowering agents
3) an increased emphasis on eliminating cigarette usage with increasingly effective pharmacologic and behavior treatments to discourage the habit, and
4) new antihypertensive agents along with new information on the value of established antihypertensive therapies in preserving kidney function.

Three recent randomized trials of medical therapy versus a reconstructive approach to renovascular disease are worthy of review (Table 1). In summarizing these trials generically (with allowances for differences in design, etc.), angioplasty had a lesser medication requirement compared with the medication-only groups, especially for bilateral renovascular disease. In the Webster study there were no differences in blood pressure outcome in the unilateral renovascular disease subjects.[3] The usual improvement in the angioplasty group is manifested by a reduction in the number of defined daily dosages (DDDs) of medications. There are few "cures" of hypertension by angioplasty in those with renovascular disease and elevated blood pressure readings. Bearing in mind that subjects in these studies were typically hypertensive while taking at least 2 drugs to qualify for these studies, this handicaped the med-

(Continued on Page 5)

Table 1 Recent Studies Comparing Angioplasty and Medical Therapy in Hypertensives with RAS

Author (reference #)	Webster[3]	Plouin[4]	Van Jaarsveld[5]
Year published	1998	1998	2000
Comparison	Angioplasty vs. Med	Angioplasty vs. Med	Angioplasty vs. Med
Number eligible	135	76	169
Number randomized	55	49	106
Age (eligible) in years	≈60 (≤75)	59 (<75)	≈60 (18-75)
Intervention (n)	Angioplasty (25)	Angioplasty (23)	Angioplasty (56)
Medical Therapy	Medication (30)	Medication (26)	Medication (50)
Definition of RAS	≥50%	≥75% (60-74%)[c]	≥50%
Follow up period	12 months	6 months	3 months[d]
BP Outcomes (mm Hg)			
Unilateral RAS		(Only Unilateral)	(Comb. Uni + Bil)
Intervention Pre	179/99	151/91 (ABPM)	179/104
Intervention Post	173/95	140/81 (ABPM)	169/99
Medical Therapy Pre	171/90	149/89 (ABPM)	180/103
Medical Therapy Post	161/88	141/84 (ABPM)	176/101
Bilateral RAS		—	(Combined)
Intervention Pre	185/94	—	—
Intervention Post	152/83[a]	—	—
Medical Therapy Pre	179/93	—	—
Medical Therapy Post	171/91	—	—
Major Event: Interv. (%)	9/25 (36%)	Not stated	Not stated
Major Event: Med. (%)	14/30 (48%)	Not stated	Not stated
Complications: Interv.	11/40[b]	6/23	6/56
Complications: Med.	Not stated	2/26	24/50
Medication Use: Interv.	Not stated	1.33/1.0[a] (Pre/Post DDD)[e]	3.3/2.5
Medication Use: Med.	Not stated	1.33/1.78 (Pre/Post DDD)	3.2/3.1

[a] $P<0.01$ compared with Medical Therapy Post
[b] Includes subjects in from a non-randomized angioplasty group
[c] Subjects with this degree of stenosis were included in study if they had a lateralizing test such as renal vein renin activity or a scintigram
[d] Data presented at 3 months; many 'Medical Therapy' subjects crossed over to angioplasty after 3 months
[e] Pretreatment and Post-treatment Defined Daily Doses of Medications
RAS=renal artery stenosis (atherosclerotic in all three studies); ABPM=ambulatory blood pressure monitor; DDD=defined daily dose of medication (e.g. 50 mg of atenolol daily = 1 DDD)

ication-only group because it selected out those with renovascular disease who responded well in the past to dual agent therapy. In the Plouin study, which limited enrollment to unilateral renal artery stenosis (RAS) only, the improvement after angioplasty was predominantly in the amount of medication needed each day.[4] The improvement in blood pressure was numerically better (-11/-10 mm Hg) in the angioplasty group than in the medical therapy group (-8/-5) but these data were not statistically significant.

In the van Jaarsveld study, clearly the more controversial of the three because of the substantial number of patients (22 of 50) who crossed over from the medical treatment group into the angioplasty group after 3 months of followup (as required as an option by their IRB approval), the improvement in blood pressure was again numerically better (-10/-5 mm Hg) in the angioplasty than the medical therapy group (-4/-2) but, again, not statistically significant.[5]

Taken together, these data cast some doubt on a clearly superior designation for renal vessel angioplasty in hypertensive patients with renovascular disease. This appears to be more the case for unilateral than bilateral disease. The treatment choice in individuals is always guided by their particular circumstances, but the existing data justify the contention that some patients with renovascular disease can be managed conservatively.

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HYPERTENSION IN PARENCHYMAL RENAL DISEASE

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Overview

Renal parenchymal disease (RPD) is the most common cause of secondary hypertension, responsible for about 4% of all patients with hypertension.[1] RPD frequently progresses to end stage renal disease, irrespective of the underlying inciting event or cause. Progressive loss of kidney function is usually accompanied by further increases in the incidence of elevated blood pressure, as shown in the Modification of Diet in Renal Disease (MDRD) study in which the frequency of hypertension rose from 66% in those with the highest glomerular filtration rate (GFR) to 95% in those with the lowest GFR.[2] Hypertension, in turn, accelerates the decline in renal function. Thus, the kidney becomes both the "victim" and the "villain",[3] and hypertension a consequence and cause of renal function loss.

Pathophysiology

With declining renal function, the kidney's ability to regulate extracellular fluid volume (ECFV), metabolize vasoconstrictors such as endothelin or produce vasodilators like nitric oxide diminishes, which contributes to hypertension and promotes nephrosclerosis. RPD patients have increased exchangeable sodium compared with essential hypertensives, with an increased ECFV.[4] Thus, hypertension in RPD is usually a volume dependent form and low levels of plasma renin activity would be expected. However, higher renin activity and angiotensin II, despite the volume overload, is sometimes noted.[4] In addition to vasoconstriction, angiotensin II augments sodium reabsorption, stimulates fibrogenic growth factors like transforming growth factor-beta, and contributes to loss of renal function through factors that increase matrix deposition. Recent evidence indicates that endothelin plays a role in hypertension and progressive renal impairment and selective endothelin antagonists should soon further define this role.

Proteinuria makes the hypertension of PRD unique. The amount of proteinuria significantly affects the progression of chronic renal insufficiency. Drugs that reduce proteinuria appear to be advantageous in preserving renal function in hypertensive patients.[5] The interrelationships of blood pressure, kidney function and proteinuria are shown in Figure 2.

Treatment

Current blood pressure goals in RPD are <130/85 mm Hg.[5] Studies such as MDRD argue for lower values such as <125 mm Hg systolic.[2] Ethnic differences in blood pressure effects on kidney function are under study in the African American Study of Kidney Disease and Hypertension (AASK trial), and treatment goals in hypertensive African Americans with chronic renal insufficiency (CRI) may be as low as 120 mm Hg systolic.

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Lifestyle modifications similar to those recommended by JNC VI with greater emphasis on sodium intake reduction (to 2 gm [88 mmol] of Na^+ daily) are warranted because of the role of sodium in blood pressure in RPD. Home weight monitoring is helpful to maintain an "ideal weight" when peripheral edema is present.

Diuretics are usually necessary to manage hypertension, although potassium sparing diuretics are usually not needed. Loop diuretics (creatinine >2.0 mg/dL) and thiazides (creatinine <2.0 mg/dL) are recommended. In some cases the addition of metolazone adds more effective diuresis compared with either of these agents alone.[5]

ACE inhibitors deserve special consideration in treatment because they appear to reduce proteinuria and the rate of renal function decline in a manner that may be independent of their antihypertensive effect.[5] Angiotensin receptor blockers are often substituted for ACE Inhibitors in individuals intolerant to the latter. Calcium-channel blockers (CCBs) are useful, although some CCBs (e.g., dihydropyridines) do not share the favorable characteristics of ACE inhibitors on proteinuria. They can improve blood pressure control further when patients are already on considerable doses of a diuretic and an ACE inhibitor and, yet, not at goal blood pressure. Other agents, such as antiadrenergic drugs and vasodilators, are also useful, particularly when treating comorbid conditions such as angina or migraine headaches.

Summary

Reducing blood pressure in RPD patients can preserve kidney function and protect other target organs such as the heart and brain. When treating the hypertension of RPD it is often necessary to use 3 or more agents to establish and maintain blood pressure goal, particularly in patients with more advanced degrees of CRI. Current practice in this regard is generally to use an antirenin drug, a diuretic and, frequently, a calcium-channel antagonist or an antiadrenergic agent.

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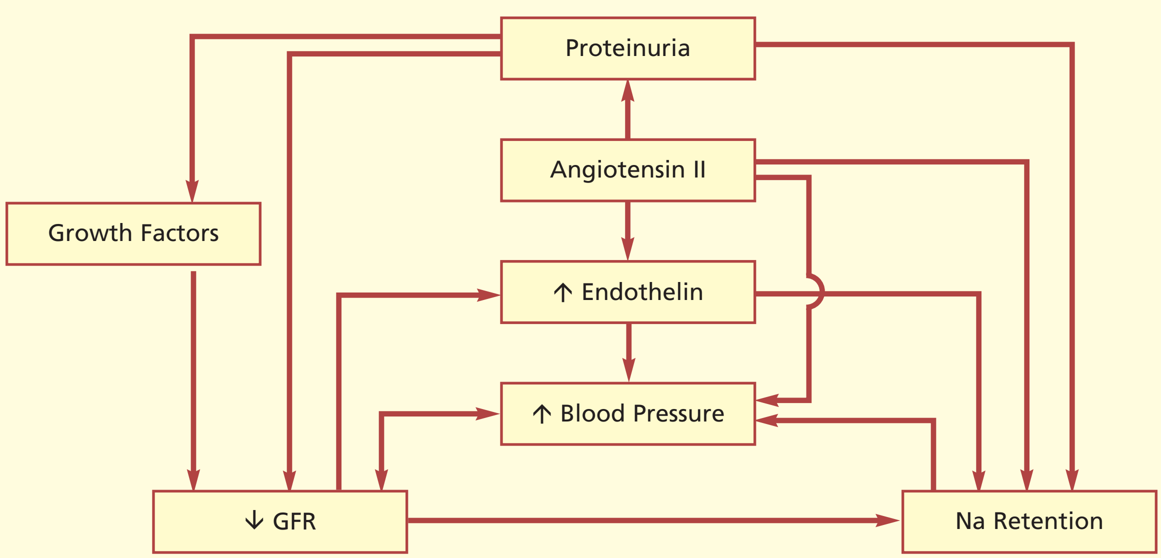
Figure 2 Graphic Presentation of the Central Role of Blood Pressure in the Interrelationship of Kidney Function, Proteinuria and Sodium (Na) Retention



GFR=glomerular filtration rate