29. Schubert DSP, Miller SI. Differences between the lower social classes: some new trends. Am J Orthopsychiatry. 1980; 50:712-7.
30. Lorion RP. Socioeconomic status and traditional treatment approaches reconsidered. Psychol Bull. 1973; 79:263-70.
31. Langsley DG. The community mental health center: does it treat patients? Hosp Commun Psychiatry. 1980; 31:815-9.
32. Braun P, Kochansky G, Shapiro R, et al. Overview: deinstitutionalization of psychiatric patients, a critical review of outcome studies. Am J Psychiatry. 1981; 138:736-49.
33. Musto D. Whatever happened to "community mental health?" Public Interest. 1975; 39:53-79.
34. *Idem*. A short history of orthopsychiatry. In: Shore MF, Mannino FC, eds. Mental health and social change: 50 years of orthopsychiatry. New York: AMS Press, 1974:5-15.
35. Rothman DJ. Decarcerating prisoners and patients. Civil Liberties Rev. 1973; 1(1):8-30.
36. Astrachan BM, Levinson DJ, Adler DA. The impact of national health insurance on psychiatric tasks and practice of psychiatry. Arch Gen Psychiatry. 1976; 33:785-94.
37. Adler DA, Astrachan BM, Levinson DJ. A framework for the analysis of theoretical and therapeutic approaches to schizophrenia. Psychiatry. 1981; 44:1-12.
38. Lorion RP. Research on psychotherapy and behavior change with the disadvantaged: past, present and future directions. In: Garfield SL, Bergin AE, eds. Handbook of psychotherapy and behavior change: an empirical analysis. 2d ed. New York: John Wiley, 1978:903-38.
39. Haase W. Role of socioeconomic class in examiner bias. In: Riessman F, Cohen J, Pearl A, eds. Mental health and the poor. New York: Free Press, 1966:241-7.
40. Katz MM, Cole JO, Lowery HA. Studies of the diagnostic process: the influence of symptom perception, past experience, and ethnic background in diagnostic decisions. Am J Psychiatry. 1969; 125:937-47.
41. Goodman JT, Streiner DL, Woodward CA, Santa Barbara T. Factors affecting psychiatric diagnosis. Can J Public Health. 1976; 67:397-400.
42. Gross HS, Herbert MR, Knatterud GL, Donner L. The effects of race and sex on the variation of diagnosis and disposition in a psychiatric emergency room. J Nerv Ment Dis. 1969; 148:638-42.
43. Adebimpe VR. Overview: white norms and psychiatric diagnosis of black patients. Am J Psychiatry. 1981; 138:279-85.
44. Lee SD, Temerlin MK. Social class, diagnosis, and prognosis for psychotherapy. Psychotherapy. 1970; 7:181-5.
45. Umbenhauer SI, DeWitte LL. Patient race and social class: attitudes and decisions among three groups of mental health professionals. Compr Psychiatry. 1978; 19:509-15.
46. Foucault M. Madness and civilization. New York: Random House, 1965.
47. Williams DH, Bellis EC, Wellington SW. Deinstitutionalization and social policy: historical perspectives and present dilemmas. Am J Orthopsychiatry. 1980; 50:54-64.
48. Dain N, Carlson ET. Social class and psychological medicine in the United States 1789-1824. Bull Hist Med. 1959; 33:454-65.
49. Carlson ET. Nineteenth century insanity and poverty. Bull NY Acad Med. 1972; 48:539-44.

MEDICAL INTELLIGENCE

CAPTOPRIL-INDUCED FUNCTIONAL RENAL INSUFFICIENCY IN PATIENTS WITH BILATERAL RENAL-ARTERY STENOSES OR RENAL-ARTERY STENOSIS IN A SOLITARY KIDNEY

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ACUTE renal failure occasionally complicates therapy with the oral angiotensin-converting-enzyme inhibitor captopril.[1-5] A variety of mechanisms have been postulated to account for captopril-induced renal insufficiency, including direct drug nephrotoxicity,[1] hypersensitivity,[2] and renal ischemia due to rapid reductions in systemic blood pressure.[3] However, the clinical importance of these complications and the types of patients at risk have not been defined.

We describe 11 patients in whom acute renal insufficiency developed while they were receiving captopril for treatment of severe hypertension associated with either bilateral renal-artery stenosis or renal-artery stenosis in a solitary kidney. In each case, the renal insufficiency resolved promptly upon discontinuation of the drug. On the basis of evidence from previous experimental studies, we propose that this unique form of captopril-induced renal insufficiency is a functional one resulting from a disturbance in the autoregulation of glomerular filtration, and that this disturbance is consequent to blockade of the renin–angiotensin system in the presence of reduced renal-artery perfusion pressure. In view of our observation, captopril should be used with great caution in patients with bilateral renal-artery stenosis or renal-artery stenosis in a solitary kidney.

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PATIENTS AND RESULTS

Clinical and angiographic data on the 11 patients are presented in Table 1. Their ages ranged from 36 to 81 years. There were seven women and four men, all with longstanding hypertension. Renal arteriography was performed in each case but was never temporally related to the development of renal insufficiency. Seven patients had bilateral renal-artery stenoses, and four patients had renal-artery stenosis in a solitary kidney (Table 1).

Captopril was administered to all patients in divided doses, the maximum daily dose ranging from 75 to 225 mg. Table 1 lists the dose of captopril as well as other medications taken by the patients before, during, and after therapy with captopril. All patients were

Table 1. Clinical Data and Therapeutic Regimens of the Patients.

Patient No.	Age/ Sex	Renal Arteriographic Finding	Daily Captopril Dose	Other Medications (per Day)		
				Before Captopril	During Captopril	After Captopril
1	56/F	95% stenosis at origin on left; >95% at origin on right	150 mg	Hydrochlorothiazide, 50 mg Hydralazine, 300 mg Propranolol, 480 mg	Furosemide, 80 mg	Furosemide, 40 mg Minoxidil, 5 mg Nadolol, 160 mg
2	65/F	>95% stenosis bilaterally; shrunken right kidney	100 mg	Propranolol, 480 mg Hydrochlorothiazide, 50 mg	Nadolol, 120 mg Furosemide, 80 mg	Propranolol, 480 mg Ethacrynic acid, 100 mg
3	75/F	100% stenosis on right with gastroduodenal collaterals; >95% stenosis on left	100 mg	Propranolol, 240 mg Hydrochlorothiazide, 50 mg	Digoxin, 0.25 mg Furosemide, 160 mg	Digoxin, 0.25 mg Methyldopa, 1 g Hydralazine, 200 mg
4	52/M	50% stenosis on right; 100% stenosis of an accessory left	150 mg	Hydrochlorothiazide, 50 mg Propranolol, 160 mg	Furosemide, 20 mg Digoxin, 0.25 mg	Isosorbide dinitrate TEMBID, 240 mg Methyldopa, 1 g Hydralazine, 200 mg
5	56/M	95% stenosis on left; right was patent 1 yr before admission. At this admission, renal-vein renin values lateralized to the right.	200 mg	Isosorbide dinitrate, 120 mg Furosemide, 120 mg Clonidine, 0.9 mg Nitropaste, 6.4 cm Hydralazine 300 mg	Isosorbide dinitrate, 120 mg Nitropaste, 6.4 cm	Isosorbide dinitrate, 160 mg Furosemide, 120 mg Clonidine, 0.9 mg
6	68/M	95% stenosis bilaterally	150 mg	Furosemide, 40 mg Hydrochlorothiazide, 50 mg Triamterene, 50 mg Propranolol, 240 mg Hydralazine, 150 mg	Furosemide, 80 mg Propranolol, 240 mg	Propranolol, 240 mg
7	68/M	>95% stenosis bilaterally	75 mg	Furosemide, 20 mg Hydrochlorothiazide, 50 mg Propranolol, 80 mg Hydralazine, 75 mg Methyldopa, 1.5 g	Furosemide, 40 mg Propranolol, 80 mg	Hydrochlorothiazide, 50 mg Nadolol, 40 mg Hydralazine, 200 mg
8	59/F	95% stenosis on right; contralateral nephrectomy	225 mg	Propranolol, 480 mg Chlorthalidone, 50 mg	Propranolol, 480 mg Chlorthalidone, 50 mg	Propranolol, 480 mg
9	52/F	95% stenosis on left; contralateral nephrectomy	150 mg	Hydrochlorothiazide, 50 mg Methyldopa, 1 g	Furosemide, 40 mg Methyldopa, 1 g	Furosemide, 200 mg Methyldopa, 1 g (Captopril continued at 75 mg/day)
10	36/F	95% stenosis of the left common iliac artery supplying renal allograft	150 mg	Prednisone, 20 mg Azathioprine, 100 mg Furosemide, 20 mg	Prednisone, 20 mg Azathioprine, 100 mg Furosemide, 20 mg	Prednisone, 20 mg Azathioprine, 100 mg Furosemide, 20 mg
11	81/F	>90% stenosis on left; contralateral nephrectomy	75 mg	Clonidine, 0.4 mg Furosemide, 80 mg Metoprolol, 200 mg	Clonidine, 0.4 mg Furosemide, 80 mg Metoprolol, 200 mg	Clonidine, 0.4 mg Furosemide, 80 mg Metoprolol, 200 mg

taking a diuretic when captopril was initiated. No major changes in drug therapy were made during captopril treatment.

Data on blood pressure and renal function are shown in Table 2. Blood pressure was reported as the average of five determinations performed on the day before captopril initiation, at the nadir during captopril, and after discontinuation of captopril during a new drug regimen (Table 1). Urinary sediment showed no evidence of acute tubular necrosis or glomerulonephritis in any of the patients. None of them had 24-hour urinary protein excretion of more than 3.5 g. Systemic blood pressure was reduced in most patients during captopril therapy, but it was either unchanged or higher than control levels in two (Patients 1 and 3) during treatment with captopril. After discontinuation of captopril and during administration of other antihypertensive medications, all patients had substantial reductions in systemic blood pressure, as compared with control levels, yet had improved renal function during this period. Seven of the patients had some degree of renal insufficiency (serum creatinine concentration equal to or greater than 1.6 mg per deciliter [140 μmol per liter]) before the initiation of captopril. The time course between the initiation of captopril and the peak impairment in renal function ranged from four days to two months. In all cases, renal function improved within one week of stopping captopril.

Although plasma renin activities were not routinely measured, the relation of renal failure to blockade of the renin–angiotensin system was supported by the observation that renal function improved in all patients when a nonspecific vasodilator was substituted for captopril. This point was also supported by the response of Patient 2 when she was rechallenged with a different converting-enzyme inhibitor. Her renal function deteriorated (the creatinine concentration increased from 1.8 to 4.8 mg per deciliter [160 to 420 μmol per liter]) when she was placed on captopril. When the drug was discontinued, the serum creatinine concentration promptly fell to 2.4 mg per deciliter (210 μmol per liter). However, when another oral convert-

Table 2. Blood Pressure and Renal Function of Patients before, during, and after Captopril.

Patient No.	Average Blood Pressure			Blood Urea Nitrogen; Creatinine		
	Before Captopril	During Captopril	After Captopril	Before Captopril	During Captopril	After Captopril
	mm Hg			mg/dl *		
1	190/105	190/105	140/80	55; 2.3	67; 4.1	27; 1.3
2	230/110	175/85	170/82	40; 1.8	119; 4.8	31; 2.4
3	180/102	210/100	140/80	37; 2.1	83; 7.0	48; 2.5
4	210/72	140/70	180/70	9; 1.2	37; 2.4	Died †
5	200/130	150/80	170/110	81; 3.1	113; 7.2	93; 3.7
6	210/110	180/90	185/95	38; 1.8	61; 3.4	32; 1.8
7	200/105	160/85	190/85	35; 1.5	119; 5.3	34; 2.0
8	220/120	168/90	168/90	33; 1.7	236; 9.6	45; 2.2
9	220/120	185/85	200/100	22; 1.3	90; 3.3	42; 1.6
10	160/95	125/80	130/80	18; 1.2	50; 2.8	30; 1.7
11	260/100	200/100	180/90	77; 4.1	131; 6.8	100; 4.4

*To convert blood urea nitrogen values to millimoles per liter, multiply by 0.357. To convert creatinine values to micromoles per liter, multiply by 88.4.

†Death followed acute renal failure, which developed after venography.

ing-enzyme inhibitor (MK421) was administered, acute renal insufficiency recurred (the creatinine level increased to 7.8 mg per deciliter [690 μmol per liter]). The serum creatinine level declined to 2.5 mg per deciliter (220 μmol per liter) when MK421 was stopped (Fig. 1).

Discussion

We suggest that these 11 cases of transient renal insufficiency may be examples of a functional disturbance in the autoregulation of glomerular filtration caused by captopril in the presence of marked reductions in renal-artery perfusion pressure. Evidence from experimental studies indicates that the renin–angiotensin system plays an important part in the autoregulation of renal blood flow and the glomerular filtration rate when renal-artery perfusion pressure is substantially reduced.[6-9] Since glomerular-capillary hydraulic pressure is determined by the balance between afferent (preglomerular) and efferent (postglomerular) vascular tone, efferent arteriolar constriction serves to maintain an effective filtration pressure and glomerular filtration rate when renal arterial perfusion pressure is substantially diminished. The critical role of the renin–angiotensin system in mediating this efferent arteriolar constriction is suggested by studies in animals in which glomerular filtration was impaired during infusions of an angiotensin antagonist, [Sar[1], Ile[8]] angiotensin II,[7] or teprotide,[9] a parenterally administered converting-enzyme inhibitor. The failure to autoregulate the rate of filtration during pharmacologic blockade of the renin–angiotensin system was exaggerated by prior sodium depletion.[7,9]

Extrapolating from the above experimental data,[7] one may clinically anticipate the generation of a functional form of acute renal failure when the renin–angiotensin system is blocked and the prevailing renal parenchyma is perfused at a sufficiently low pressure. As our observations suggest, this set of conditions is apparently satisfied when captopril is administered to patients with hemodynamically severe renal-artery stenosis involving either both renal arteries or the renal artery of a solitary kidney, whether native or transplanted. Severe unilateral renal-artery stenosis in the presence of a contracted, atrophic contralateral kidney would also be expected to result in this functional decrement in glomerular filtration rate. Depending on the severity of the renovascular stenoses, in some patients captopril must produce a certain decrease in systemic blood pressure before renal perfusion pressure becomes critically reduced. On the other hand, in patients with extreme degrees of renovascular stenosis and thus profoundly depressed renal perfusion pressure, systemic arterial pressure need not decrease after captopril treatment for the phenomenon to develop; blockade of the intrarenal action of the renin–angiotensin system would be cause enough. In these patients, the contribution of the non-renin–angiotensin actions of captopril (i.e., through prosta-

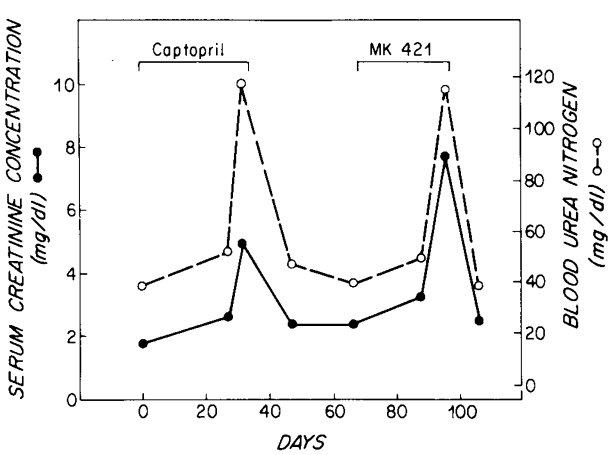

Figure 1. Responses of Serum Creatinine and Blood Urea Nitrogen to the Converting-Enzyme Inhibitors Captopril and MK421 in Patient 2.

To convert creatinine values to micromoles per liter, multiply by 88.4. To convert blood urea nitrogen values to millimoles per liter, multiply by 0.357.

glandins or kinins[10-12]) to intrarenal hemodynamics cannot be ruled out.

By contrast, administration of captopril to patients without renal-artery stenosis would not be expected to result in such functional reductions in filtration rate because, unless critical systemic hypotension develops, renal-artery perfusion pressure should remain within the range in which autoregulation of glomerular filtration is not dependent on an intact renin–angiotensin mechanism. Similarly, the development of clinically evident reductions in glomerular filtration rate would not be anticipated after captopril treatment in patients with unilateral renal-artery stenosis and a well-preserved normal contralateral kidney.[5]

We believe that the evidence cited above is relevant to the pathogenesis of acute renal insufficiency in our patients. Although renal biopsies were not performed, there was little clinical evidence to suggest renal-parenchymal injury. Serial examinations of urinary sediment did not suggest acute tubular necrosis. None of our patients had skin rash, eosinophilia, or other evidence of drug hypersensitivity.[2] Captopril has been associated with the development of membranous glomerulopathy,[13-15] but our patients had no clinical evidence of this. Although a direct nephrotoxic effect of captopril cannot be entirely ruled out in the absence of renal biopsies, we believe that the renal insufficiency in our patients was functional in nature. We do not think that the renal failure was due solely to a lowering of blood pressure, since it did not occur when comparable or greater reductions in blood pressure were achieved with other antihypertensive regimens (Table 2). Our hypothesis is further supported by the observation that the renal function of Patient 2 deteriorated after challenge with a structurally dissimilar converting-enzyme inhibitor (MK421).[16]

Diuretics may have had a contributory role, since sodium depletion may increase the dependency of the glomerular filtration rate on an intact renin–angiotensin system and sensitize the patient to the development of a functional form of acute renal failure after angiotensin blockade. The variable period before the onset of renal insufficiency appears to be closely related to the concomitant volume status of the patient. It may be that a certain degree of volume contraction is necessary for the development of this phenomenon. Preexisting renal insufficiency may also be a risk factor. Moreover, it should be noted that none of our patients received any other potentially nephrotoxic agents or prostaglandin synthetase inhibitors (e.g., indomethacin or aspirin) during captopril administration. Finally, the functional character of the suggested captopril-mediated renal insufficiency is strongly supported by the fact that in each of our patients the decrements in glomerular filtration rate promptly resolved when captopril was discontinued. To confirm our hypothesis, future controlled studies comparing the effects of captopril treatment and other antihypertensive regimens on renal hemodynamics in this setting will be necessary.

The prevalence of captopril-induced renal insufficiency under these circumstances is currently unknown. Until prospective clinical trials settle this question, we believe that the presence of bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney constitutes a substantial risk. If captopril must be used in these settings, diuretics should be used with caution and renal function should be monitored closely. The development of acute renal insufficiency during captopril therapy in a patient not already known to have such lesions should raise the suspicion of underlying renal-artery stenoses.

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References

1. Farrow PR, Wilkinson R. Reversible renal failure during treatment with captopril. Br Med J. 1979; 1:1680.
2. Luderer JR, Schoolwerth AC, Sinicrope RA, Ballard JO, Lookingbill DP, Hayes AH Jr. Acute renal failure, hemolytic anemia and skin rash associated with captopril therapy. Am J Med. 1981; 71:493-6.
3. Collste P, Haglund K, Lundgren G, Magnusson G, Ostman J. Reversible renal failure during treatment with captopril. Br Med J. 1979; 2:612-3.
4. Grossman A, Eckland D, Price P, Edwards CRW. Captopril: reversible renal failure with severe hyperkalaemia. Lancet. 1980; 1:712.
5. Hollifield JW, Moore LC, Winn SD, et al. Angiotensin converting enzyme inhibition in renovascular hypertension. Cardiovasc Rev Rep. 1982; 3:673-6.
6. Dzau VJ, Siwek LG, Rosen S, Farhi ER, Mizoguchi H, Barger AC. Sequential renal hemodynamics in experimental benign and malignant hypertension. Hypertension. 1981; 3: Suppl:1:I-63-8.
7. Hall JE, Guyton AC, Jackson TE, Coleman TG, Lohmeier TE, Trippodo NC. Control of glomerular filtration rate by renin-angiotensin system. Am J Physiol. 1977; 233:F366-72.
8. Hall JE, Guyton AC, Cowley AW Jr. Dissociation of renal blood flow and filtration rate autoregulation by renin depletion. Am J Physiol. 1977; 232:F215-21.
9. Hall JE, Colemen TG, Guyton AC, Balfe JW, Salgado HC. Intrarenal role of angiotensin II and [des-Asp^1]angiotensin II. Am J Physiol. 1979; 236:F252-9.
10. Johnston CI, Millar JA, McGrath BP, Matthews PG. Long-term effects of captopril (SQ14 225) on blood-pressure and hormone levels in essential hypertension. Lancet. 1979; 2:493-6.
11. Brunner HR, Gavras H, Waeber B, et al. Oral angiotensin-converting enzyme inhibitor in long-term treatment of hypertensive patients. Ann Intern Med. 1979; 90:19-23.
12. Swartz SL, Willams GH, Hollenberg NK, Levine L, Dluhy RG, Moore TJ. Captopril-induced changes in prostaglandin production: relationship to vascular responses in normal men. J Clin Invest. 1980; 65:1257-64.
13. Case DB, Atlas SA, Mouradian JA, Fishman RA, Sherman RL, Laragh JH. Proteinuria during long-term captopril therapy. JAMA. 1980; 244:346-9.
14. Kincaid-Smith P, Whitworth JA, Walter NMA, Dowling JP. Immune complex glomerulopathy and captopril. Lancet. 1980; 2:37.
15. Hoorntje SJ, Weening JJ, Kallenberg CGM, Donker AJM. Serum-sickness-like syndrome with membranous glomerulopathy in patient on captopril. Lancet. 1979; 2:1297.
16. Gavras H, Biollaz J, Waeber B, Brunner HR, Gavras I, Davies RO. Antihypertensive effect of the new oral angiotensin converting enzyme inhibitor "MK-421." Lancet. 1981; 2:543-7.