State-of-the-Art Review: Captopril Renography—Pathophysiological Considerations and Clinical Observations

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Advances in renal angiography and revascularization techniques have renewed interest in developing a better noninvasive screening test for identifying patients with potentially correctable renovascular hypertension. Captopril renography is a promising diagnostic tool in the evaluation of the hypertensive patient. This review highlights the important pathophysiological changes in renal hemodynamics and humoral response attributable to significant renal artery stenosis, and underscores the dramatic effects of angiotensin-converting enzyme inhibition on the renovascular bed. The review also summarizes the available clinical information in captopril renography, and presents consensus recommendations on appropriate patient selection, radionuclide(s) of choice, and suggested diagnostic criteria.

HYPERTENSION affects nearly 60 million Americans and poses a tremendous health risk. Hypertensive cardiovascular disease is a leading cause of death in the United States. Renovascular hypertension (RVHT) remains the major cause of potentially curable hypertension. Advances in percutaneous transluminal renal angioplasty (PTRA) and surgical techniques have renewed interest in developing a better screening test for identifying patients with potentially correctable RVHT. The combination of radionuclide studies of the kidney with angiotensin-converting enzyme (ACE) inhibition using captopril has shown promise for improving the noninvasive detection of significant stenosis of the renal artery. This review focuses on both the alterations in renal physiology in renal artery stenosis (RAS), which are clinically relevant to the interpretation of captopril renography in the evaluation of hypertension, and the results of the pertinent clinical studies to date.

PHYSIOLOGY OF RAS

Constricting the main renal artery leads to a cascade of important hemodynamic and humoral responses within the kidney distal to the stenosis.[1] Constriction of the renal artery results in initial vasodilatation distal to the stenosis in an attempt to maintain blood flow. If stenosis is severe, there is a transient decrease in distal renal artery pressure and blood flow. This autoregulatory vasodilatation is short-lived because the decrease in renal perfusion pressure stimulates renin release and the generation of intrarenal angiotensin II (A II). A II produces renal vasoconstriction, which attenuates this reduction in renal blood flow. If a similar constriction is reproduced during ACE inhibition, the A II-dependent increase in renovascular resistance is blocked, and renal artery pressure and blood flow remain low. In addition to these important effects on renovascular resistance and blood flow, A II also exerts a powerful influence on maintaining glomerular filtration rate (GFR) by inducing preferential efferent arteriolar vasoconstriction. However, constriction in the presence of ACE inhibition results in a severe reduction in GFR, and highlights the prominent role of A II in maintaining GFR, renal blood flow, and systemic blood pressure.

EFFECTS OF ACE INHIBITION

Understanding the effects of ACE inhibition on the kidney ipsilateral to the stenosis, as well as on the contralateral kidney, is crucial in anticipating the changes in the radionuclide studies of the kidney following ACE inhibition. RVHT appears to be dependent on renin secretion from the juxta-glomerular apparatus of the underperfused, stenotic kidney, and is partially maintained by participation of the contralateral kidney, which demonstrates an abnormal pressure-natriuresis relationship in which a new set point of sodium homeostasis is attained at a higher level of arterial pressure. ACE inhibition

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acts to interrupt the renin-angiotensin-aldosterone system (RAAS) pathway by preventing the conversion of the decapeptide angiotensin I (A I) to the octapeptide A II so that both the vasoconstrictor-hemodynamic and aldosterone-stimulating effects of A II are blocked (Fig 1). Hence, ACE inhibition acts as a pharmacological probe to investigate the role of A II in the pathophysiology of RVHT. The provocative challenge of the ACE inhibitor, captopril, has been studied in two fashions. As seen in Fig 1, administration of the ACE inhibitor blocks the conversion of A I to A II so that the concentration of renin, which is proximal to the blockade, may increase. In fact, patients with RVHT have a marked hyperreninemic response to captopril stimulation compared with patients with essential hypertension. This pathophysiology forms the basis of the captopril plasma renin activity test described by Muller et al.[2] Second, blockade of the renin-angiotensin cascade with the ACE inhibitor markedly attenuates the generation of A II, which has measurable effects on both systemic blood pressure and intrarenal hemodynamics. The latter effect forms the physiological basis of the captopril-stimulated renography studies. An understanding of the effect of ACE inhibition on renal hemodynamics and function is critical to an understanding of captopril renography.

Unilateral RAS

The effects of ACE inhibition on the stenotic and contralateral kidney have been studied extensively in the classic model of renin-dependent hypertension, ie, the two-kidney,

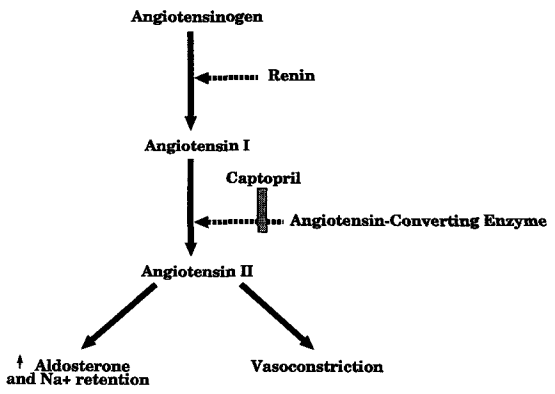

Fig 1. Schematic of the RAAS showing the cascade of events leading to vasoconstriction.

one-clip (2K, 1C) model of Goldblatt hypertension, which is analogous to unilateral RAS. It is important to note the contrasting effects that this blockade has on the stenotic and the seemingly normal contralateral kidney. In the animal model of 2K, 1C Goldblatt hypertension, ACE inhibition results in a significant pressure-associated decrease in GFR, urine flow, and salt excretion of the clipped kidney.[3] It is also widely recognized that the effects of ACE inhibition in this model are not confined to the stenotic kidney. Despite the reduction in arterial pressure with ACE inhibition, the nonclipped contralateral kidney exhibits dramatic increases in GFR, urine flow, and salt excretion that would suggest contralateral renal vasodilatation. It is speculated that this contralateral vasodilatation may result from the reduction in the vasoconstrictor effects of circulating A II synthesized in the stenotic kidney. Overall, ACE inhibition in experimental models of unilateral RAS demonstrates a reduction in mean arterial pressure associated with a diminution of the function of the stenotic kidney and the contralateral kidney exhibits an increase in GFR, renal blood flow, and excretory function. These expected physiological changes within the stenotic and contralateral kidneys following ACE inhibition are the basis of the asymmetry of renal function detected by renal scintigraphy, and should help improve the noninvasive diagnosis of unilateral RAS.

These observations highlight the important role that A II plays in regulating renal hemodynamics and function in RAS. The rationale for the captopril-stimulated radionuclide studies is that the ACE inhibitor captopril reduces the A II-dependent efferent arteriolar resistance, which results in a reduction in transcapillary forces, therefore reducing renal function in the kidney distal to the stenosis (Fig 2). When renal perfusion is reduced, as seen in RAS (Fig 2B), the transcapillary pressures that maintain the forces to drive glomerular filtration are sustained by a preferential increase in efferent arteriolar resistance. This increased efferent arteriolar resistance is maintained via A II. Captopril acts to block the formation of A II, and consequently reduces the postglomerular efferent resistance and diminishes transcapillary forces maintaining filtration, thus decreas-

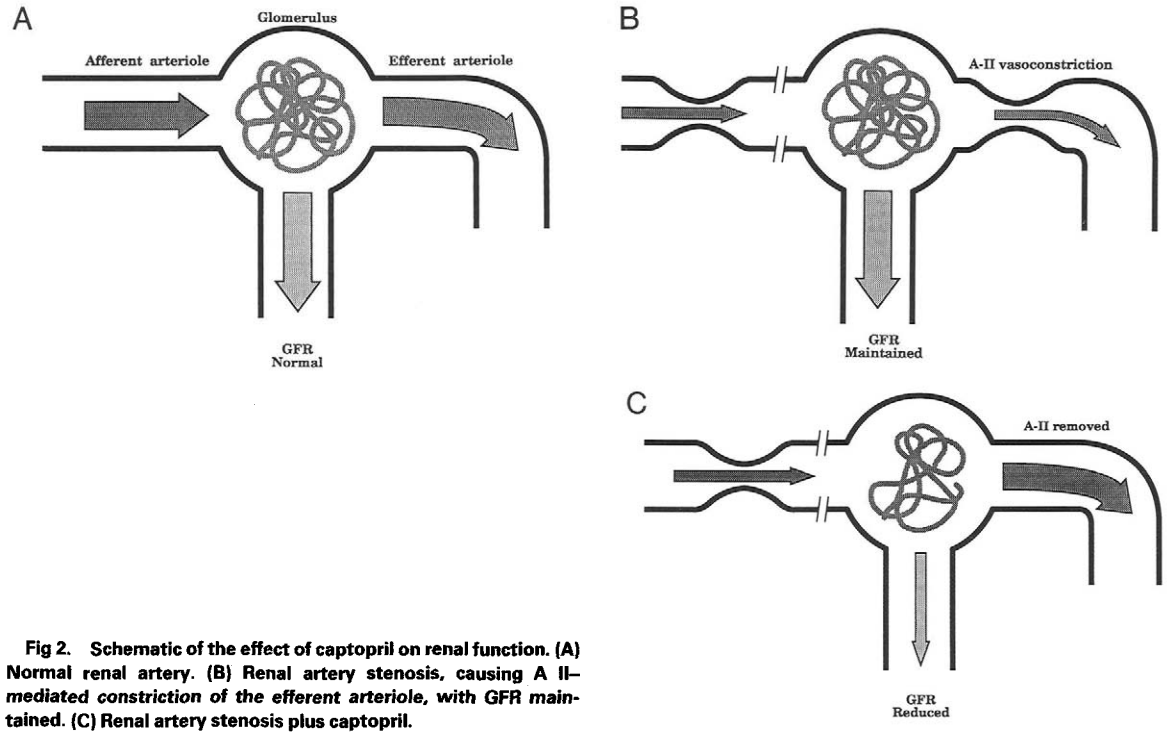

Fig 2. Schematic of the effect of captopril on renal function. (A) Normal renal artery. (B) Renal artery stenosis, causing A II–mediated constriction of the efferent arteriole, with GFR maintained. (C) Renal artery stenosis plus captopril.

ing the GFR of the stenotic kidney (Fig 2C). This decrement in individual kidney function may then be assessed noninvasively using conventional radionuclide studies.[4]

Observations in experimental models of Goldblatt hypertension have demonstrated a relationship between changes in the radionuclide studies with changes in renal function following ACE inhibition. In the experimental canine model of 2K, 1C hypertension, Nally et al[5] demonstrated that captopril lowered mean arterial pressure (MAP) and produced striking alterations in the time-activity curves of both the technetium-99m (^{99m}Tc) diethylenediaminepentaacetic acid (DTPA) and iodine-131 (^{131}I) orthoiodohippurate (OIH) renograms (Fig 3). These changes correlated with a 30% reduction in GFR of the kidney distal to the stenosis (Fig 4). Captopril did not further reduce the effective renal plasma flow (ERPF) in the clipped kidney, and ERPF of the normal contralateral kidney rose by 22% despite a 20% reduction in arterial pressure (Fig 4B). These changes in the renograms were reversible (Fig 3D), and did not occur when MAP was lowered with the nonspecific vasodilator sodium nitroprusside (Fig 3E). These data support the hypothesis that ACE inhibition removes the A II-dependent efferent arteriolar resistance, thereby reducing the transcapillary forces maintaining GFR of the affected kidney. Subsequent studies in the same model provide additional support for this hypothesis. Administration of the competitive A II antagonist, saralasin, produced similar but less striking reductions in MAP, GFR, and changes in the renogram, perhaps related to either inadequate dosage or the mild A II agonistic effect of saralasin.[6] In contrast, lowering the MAP with either sodium nitroprusside or atrial natriuretic factor (ANF) did not produce changes in the renogram or kidney function. Of interest, administration of the calcium channel blocker, verapamil, lowered MAP and produced striking reductions in both kidney function and renography.[7] These changes with the various vasoactive agents are summarized in Table 1. These observations emphasize that the changes in the radionuclide studies of the individual kidneys correlate with the transient reduction of GFR and not with the simple lowering of MAP by the various vasoactive agents. Furthermore, captopril also can produce dramatic alter-

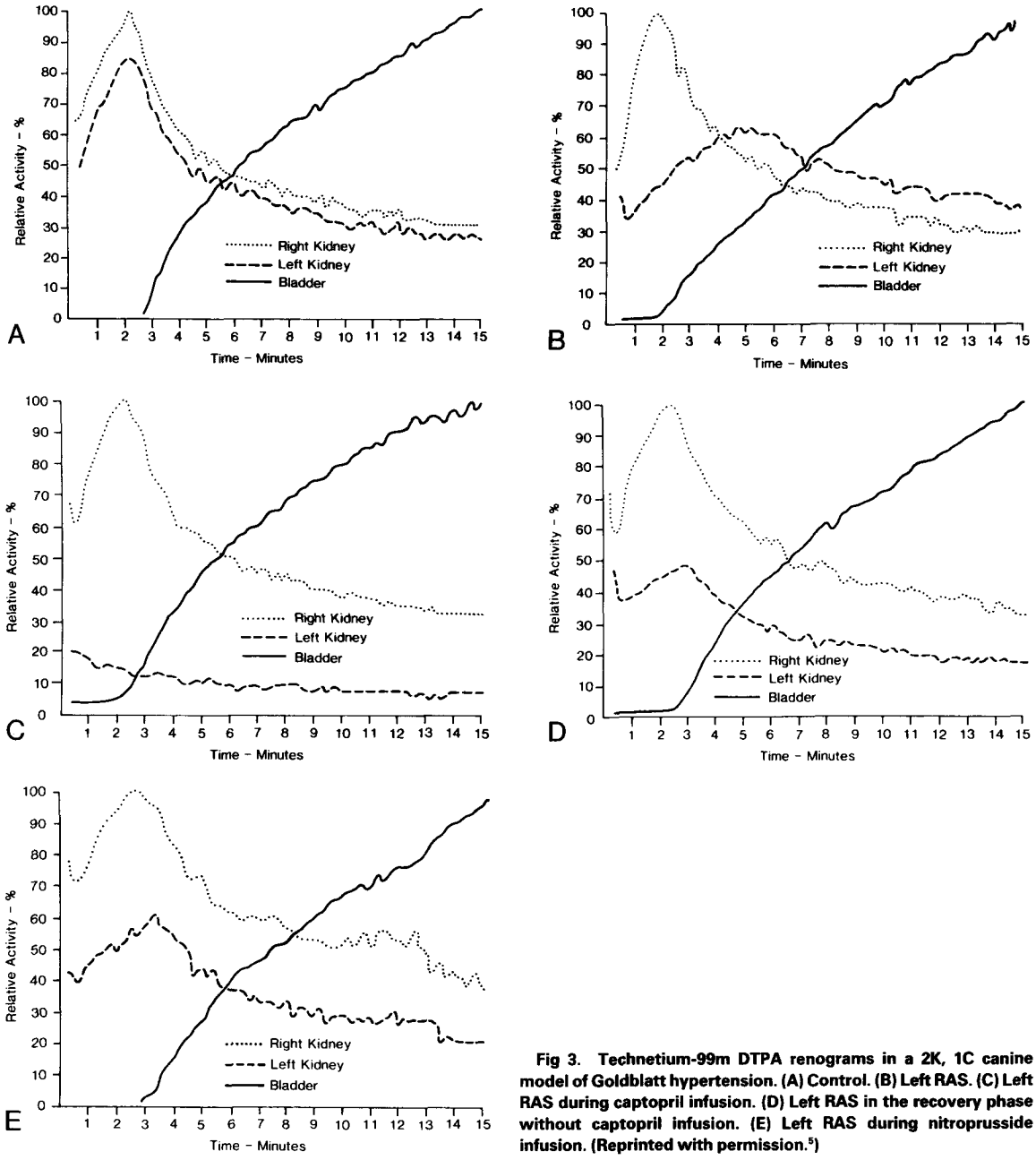

Fig 3. Technetium-99m DTPA renograms in a 2K, 1C canine model of Goldblatt hypertension. (A) Control. (B) Left RAS. (C) Left RAS during captopril infusion. (D) Left RAS in the recovery phase without captopril infusion. (E) Left RAS during nitroprusside infusion. (Reprinted with permission.[5])

ations in [^{131}I]OIH or ^{99m}Tc mercaptoacetyltriglycine (MAG_3) renograms despite insignificant changes in measured ERPF of the kidney distal to the stenosis. The pattern of change usually involves cortical retention of the radionuclide, as originally reported by Sfiakanikis,[8] and apparently relates to the marked reduction of tubular flow with stasis and cortical retention of the radionuclide following the ACE inhibitor–induced reduction in ipsilateral GFR.

Bilateral RAS

Clearly, captopril-stimulated renography in experimental and clinical studies has been most impressive in the most widely recognized form of RVHT, namely, unilateral RAS. With bilat-

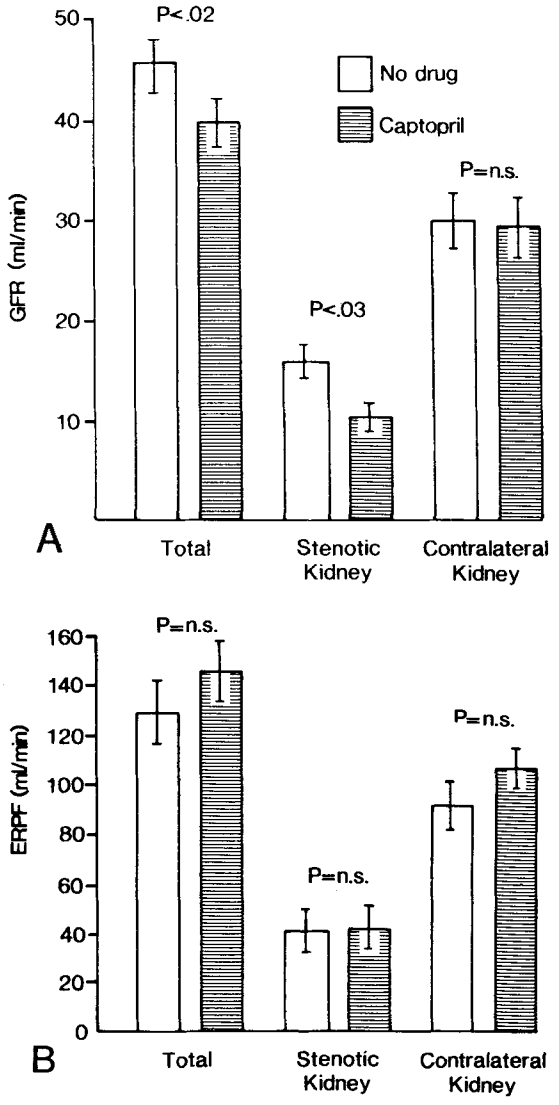

Fig 4. Effect of captopril on kidney function in 2K, 1C Goldblatt hypertension. (A) GFR. (B) ERPF. (Reprinted with permission.[5])

eral RAS, it was postulated that the detection of stenosis may be more complicated for two reasons. First, the exaggerated degree of asymmetry of renal function in response to ACE inhibition may be diminished since both kidneys may behave in a "clipped" fashion. Second, coexisting renal insufficiency secondary to advanced renovascular disease might compromise the ability of some radionuclides, such as [^{99m}Tc]DTPA, to accurately assess the changes in renal function.

In a canine model of two-kidney, two-clip hypertension, recent studies demonstrate that captopril lowered MAP and produced striking changes in the time-activity curve of each kidney.[9] Furthermore, the changes in the renogram were more pronounced in the more severely stenotic kidney, and correlated with the greater reduction in GFR and enhanced renal vein renin determinations of that kidney following captopril stimulation. These studies imply that captopril-stimulated renography may be a suitable noninvasive tool to replace the invasive renal vein renin measurements to determine the more severely stenotic kidney in patients with bilateral RAS. To date, preliminary studies in a small number of patients with bilateral RAS have demonstrated similar results, yet more comprehensive studies are required.

Table 1. Effect of Vasoactive Agents in 2K, 1C Hypertension

	MAP	GFR (SK)	[^{99m}Tc]DTPA	Hippuran
Captopril	↓ ↓ ↓	↓ ↓ ↓	****	***
Nitroprusside	↓ ↓ ↓	NA	↔	↔
ANF	↓ ↓ ↓	↔	↔	↔
Saralasin	↓	± ↓	**	**
Verapamil	↓ ↓ ↓	↓	***	***

SK, stenotic kidney; ↓, decrease; ↔, no change; NA, not available; *, degree of abnormality.

Solitary-Kidney RAS

In a solitary kidney with stenosis, the issue of degree of renin dependency of blood pressure and renal function remains controversial. Traditionally, the 1K, 1C model has been viewed as a volume-dependent (low renin) rather than renin-dependent form of hypertension. In a sodium-replete canine 1K, 1C model, captopril reduced MAP but did not significantly alter the GFR and ERPF; neither did [^{99m}Tc]DTPA or [^{131}I]OIH renography.[10] In contrast, Lee and Blaufox[11] reported a significant decrease in GFR following ACE inhibition in their 1K, 1C rat model. The response of blood pressure and kidney function to ACE inhibition may be a function of the degree and duration of stenosis as well as the state of sodium balance. The state of sodium balance may play a pivotal role in the activation of the RAAS. Significant sodium depletion, induced by either a low-salt diet or diuretics, may be responsible for the stimulation of the RAAS so that blood pressure and kidney function are A II dependent whether or not there is

RAS leading to that kidney. These types of physiological considerations are particularly important in designing clinical protocols and scrutinizing data generated from captopril-stimulated renography.

Implications for the Clinician

These pathophysiological concerns of renal hemodynamics and function with RAS impact directly on key questions in the clinical arena regarding the utility of captopril renography. These considerations are crucial in addressing questions of patient preparation, radionuclide(s) of choice, and diagnostic criteria in various forms of RVHT. First, the state of hydration and use of diuretics before captopril-stimulated renography is a critical issue. By inducing sodium depletion, the sensitivity of the test may improve, but the specificity in hypertensive patients without RAS may suffer. In addition, the data reviewed earlier suggest that some antihypertensive medications, such as calcium blockers, and other vasoactive agents may have a direct effect on renal hemodynamics and function or may indirectly affect these parameters via their effect on the RAAS. For example, the powerful immunosuppressive agent, cyclosporine A, may exert both direct and indirect effects and potentially alter the results of captopril renography in the hypertensive renal transplant population. Second, the effect of A II on the filtration fraction (GFR/ERPF) within the stenotic kidney may alter the extraction and renal handling of radionuclides as originally observed by Wenting et al[12] with OIH and iothalamate. Finally, it must be recognized that the initial encouraging responses of captopril renography were generally reported in selected patients with unilateral RAS, a renin-dependent model with the greatest likelihood of success. The authors will now focus on interpreting the clinical studies with captopril renography available to date with these physiological principles of RAS in mind. Although preliminary reports seem favorable, the situation demands close scrutiny of a large data base in all forms of hypertension, with and without compromised renal function, before meaningful information of sensitivity and specificity of the combined technique can be computed accurately.

CLINICAL OBSERVATIONS

The effect of ACE inhibitors on the pathophysiological processes described above, and the ability of renography accurately to image these changes, make captopril renography a particularly appealing noninvasive technique both to detect and to exclude RAS. This is especially important because almost all other diagnostic tests, including the recently devised captopril test, have not proven to be sensitive or specific enough for this purpose.[2,12,13,14] Renography is safe and widely available in both the United States and abroad. The procedure is performed in one site, and does not require the collection of blood with the scrupulous handling and analysis of the sample that is so often necessary to measure plasma renin activity properly.

Saddler and Black[15] and Davidson and Wilcox[16] have recently reviewed much of the international experience with captopril renography. In addition, a supplement to the *American Journal of Hypertension* was devoted to the proceeding of the Consensus Conference on Captopril Renography held in Cleveland, OH in November 1990. This issue was published in December 1991 and includes the preliminary results of the largest trial to date, the European Captopril Radionuclide Test Multicenter Study.[17]

Virtually all of the groups that have developed and evaluated the utility of this test have been enthusiastic, and feel that it represents a very promising advance for diagnosing RAS and, perhaps, for predicting the outcome of revascularization. It is difficult to assess precisely the diagnostic accuracy of captopril renography because the protocols used by various groups are so different. In general, it has been highly sensitive (80% to 95%) and reasonably specific (50% to 94%), and compares very favorably to other techniques.

The following questions must be addressed: Which patients should be selected for study? How should the patients be prepared? What are the most appropriate radionuclide(s) and ACE inhibitors to be employed? What are the most helpful diagnostic criteria and how accurate are they?

Patients to be studied. The predictive value and clinical utility of captopril renography, as in

the situation of every diagnostic test used to find cases of an uncommon condition such as RAS, depends on the prevalence of the disease in the patients studied.[16,18-21] In a cohort where the disease is unusual, a positive test is more likely to be false positive rather than true positive. The ideal group to study is one in which the prevalence of disease is high. Consequently, captopril renography should be employed in hypertensive patients in whom there is a high index of suspicion of RVHT based on clinical clues.

Setaro et al[19] evaluated only patients whom they felt had a high likelihood of having RAS based on clinical criteria. The investigators selected (1) hypertensive patients with clinical or laboratory evidence of vascular disease in the visceral, cerebral, coronary, or ileo-femoral regions, especially if the patients had a history of current or past heavy cigarette smoking; (2) those with refractory hypertension (uncontrolled hypertension despite adequate doses of two or more appropriate antihypertensive drugs) not explained by another reason; and (3) those who had renal insufficiency without another obvious etiology. Using these criteria, the investigators were able to define a cohort with a 50% prevalence of RAS.[19] Captopril renography was 91% sensitive and 87% specific in this series.

Other groups have also been able to use clinical parameters to select high-risk patients and substantially improve the likelihood that the test would be accurate. The European Captopril Radionuclide Test Multicenter Study Group evaluated 424 patients thought to be very likely to have RAS, and 230 (54%) indeed did have a positive renal arteriogram.[17] The precise clinical features used were not specified and not necessarily the same for each of the 20 participating centers. In this study, the overall sensitivity was not as high (73% for unilateral but 91% for bilateral RAS), although the specificity was equivalent (84% overall and 92% for patients without renal insufficiency) to that of Setaro.

Svetkey et al[22] used somewhat different clinical clues to select patients for further study. They concentrated on those with grade 3 or 4 retinopathy, the recent onset of severe hypertension (diastolic blood pressure $\geq$115 mm Hg), accelerated or malignant hypertension, abdominal or flank bruits, abnormal rapid-sequence intravenous pyelograms, hypertension at a young (<25 years) or older (>45 years) age, and/or resistant hypertension. They did not specifically include patients with vascular disease, and they excluded patients with serum creatinine levels greater than 2.0 mg/dL. The frequency of positive renal arteriograms was only 24% in their cohort. Although the sensitivity of the captopril renogram was high (80 = 91%), the specificity was unacceptably low (42% to 50%). As will be discussed below, this group also analyzed the renogram in a fashion that may also explain the poor specificity of the test in their hands.

Fine et al[23] showed that captopril did not affect the renogram curves, measured with DTPA or OIH, in a group of 30 patients judged to be at very low risk of having RAS. Although none of these patients had undergone renal angiography, the patients had been followed for many years without developing any of the usual clinical features suggestive of RAS. This preliminary study suggests that there would be very few false-positive captopril renograms even in patients with presumed essential hypertension.

The Working Party Group for Patient Selection and Preparation, which met during the Captopril Renogram Consensus Conference, recommended that this test only be done in patients felt likely to have RAS on clinical grounds.[24] These characteristics include but are not necessarily limited to:

1. patients with well-documented, recent-onset hypertension, especially if diastolic blood pressure is $\geq$105 mm Hg;
2. patients with known longstanding and well-controlled hypertension, who become refractory to an existing regimen and who do not have another explanation for their resistance to treatment;
3. patients with clinical evidence of generalized vascular disease, ie, peripheral vascular disease, cerebrovascular disease, aortic occlusive disease, abdominal aortic aneurysms, and coronary artery disease, and significant hypertension;
4. patients with hypertension and abdominal bruits, regardless of the time in the cardiac cycle in which the bruit is heard;
5. patients with hypertension and an elevated serum creatinine when no other

etiology can be found to explain the renal dysfunction;

6. patients under the age of 25 who develop moderate or severe hypertension, ie, diastolic blood pressure ≥ 105 mm Hg), especially if they are white and not obese;
7. patients with refractory hypertension on an adequate three-drug antihypertensive regimen, and no other etiology can be found; and
8. patients with hypertension who develop new or more severe renal failure when treated with ACE inhibitors.

These recommendations can serve only as preliminary guidelines pending more experience and further refinements of captopril renography. In addition, two very crucial issues are not addressed. First, can captopril renography distinguish anatomic RAS from functional RAS, eg RVHT, and possibly predict the outcome of renal revascularization? Second, can the test be used to detect patients with ischemic nephropathy regardless of whether or not hypertension coexists?

It has been known for decades that patients with renal artery lesions may have a technically successful renal artery revascularization, either with surgery or PTRA, yet show no reduction in blood pressure. Moreover, other patients may have typical renal arterial lesions and not be hypertensive.[25-27] No currently available diagnostic test can precisely distinguish whether the renal artery lesion noted on the angiogram is the cause of an individual patient's hypertension.[13] The method that has been used most widely to prove that the lesion seen is functionally significant has been to compare the renal vein renin activity in both kidneys, with or without stimulation of the renin-angiotensin system.[28,29] In 1984, Rudnick and Maxwell[30] pooled the available data and showed that although the ratio of renal vein renin activity was an excellent way to predict the success of revascularization, 65% of the patients whose renal vein-renin activity ratio did not lateralize, and in whom the surgery or angioplasty would have been expected to fail, still had a favorable result. Svetkey et al[22] and Postma et al[29] confirmed the lack of value of renal vein renin ratios and also showed that the captopril test also did not predict outcome. Similarly, neither group had good results when simply using the results of captopril renography for that purpose.

In 1986, Geyskes et al[31] suggested that the *effect of captopril on the renogram* might distinguish anatomic RAS from RVHT. They have since extended this observation, and these findings have been confirmed by others.[19,32] Though promising, the authors agree with Davidson and Wilcox that these data are not yet conclusive enough to be the basis of the decision whether or not to proceed with revascularization.[16] In the studies summarized in their editorial, the best any group did using the actual results of an intervention would have denied a successful procedure to 10% to 20% of those who might have benefited. In addition, with the exception of Geyskes et al, a similar percentage of patients would have failed to be helped and would have been subjected to the risks of an intervention.[16,32] It can be said, though, that a renogram that shows an abnormality *not affected by captopril* indicates, with a reasonably high probability, that the renal artery lesion present may be associated with irreversible hypertension. Knowing this fact could certainly help the clinician and patient decide to avoid renal artery surgery or PTRA when the risk of the procedure is particularly high. In the coming years, careful attention must be paid to the utility of captopril renography in predicting the outcome of revascularization.

There are very few data on the utility of this test to find patients with ischemic nephropathy. As Ying et al[33] pointed out in 1984, some hypertensive patients with significant renal insufficiency have bilateral RAS or have a stenotic lesion in the renal artery of a solitary kidney. Since RAS does not always cause hypertension, it is also likely that there are some normotensive patients with renal failure of varying degrees who have RAS and ischemic nephropathy as the etiology.

It is not known how many patients who present for dialysis or renal transplantation have ischemic nephropathy and how many of these patients could have avoided developing end-stage renal disease if renal perfusion had been restored before irreversible damage had occurred. It is well accepted that revascularization usually fails to improve renal function when the kidney is small (< 9.0 cm).[34] Furthermore,

angiography is particularly risky in these patients, many of whom have severe atherosclerosis and are at high risk of atheroembolic disease. Thus, most nephrologists do not routinely evaluate patients looking for ischemic nephropathy, even if the clinical features suggesting RAS are present and even though there is potential for preventing the inexorable decline in renal function. The risks of angiography are simply too high and the results of revascularization in this type of patient are largely unknown to justify the evaluation. Over the next several years it will be important to see if captopril renography can distinguish which patients with mild to moderate renal failure actually have patent renal arteries, ie renal parenchymal disease, and which ones have a potentially reversible renal arterial lesion.

Unfortunately, there currently exists little information about the utility of captopril renography in patients with severe renal failure and almost none about normotensive patients with renal insufficiency. Scoble et al,[35] at the Royal Free Hospital in London, did show that captopril renography was reasonably sensitive (75%) in patients with severe renal failure (serum creatinine >300 nmol/L). In the Yale Vascular Center series, 11 patients with serum creatinine values of ≥ 3.0 mg/dL had captopril renograms done. In all patients, seven with RAS and four without, the renogram correctly predicted the findings on angiography.[36] In this entire series, an increased serum creatinine was present in 41% of the patients studied, and the test was equally sensitive and specific as it was in patients with normal renal function. Erbslöh-Möller et al[37] also showed that [^{131}I]OIH renography, using enalaprilat and furosemide, can distinguish renal parenchymal disease from ischemic nephropathy in patients with serum creatinine levels from 1.8 to 5.3 mg/dL. However, all of these patients were hypertensive, so we cannot predict whether captopril renography would be more sensitive than standard renography in normotensive patients with severely depressed renal function. Should captopril renography be a safe and effective way to exclude ischemic nephropathy, regardless of blood pressure, the patients in whom this diagnosis is suspected could be screened without the risks of angiography.

Patient preparation. Some disagreement continues as to the optimum way to prepare patients for captopril renography. All investigators agree that ACE inhibitors should be stopped before the test, although the length of time necessary is in dispute. Some groups hold them for 7 to 14 days, while others have had good results stopping for only 1 to 2 days. Other medications, with the possible exception of diuretics, can be continued without reducing the diagnostic accuracy of the test. Some have stopped diuretics for 1 to 3 days before the renogram to avoid dropping blood pressure too far when the ACE inhibitor is given. All investigators recommend oral hydration before the test, either at home or in the nuclear medicine department, and many take the precaution of having an intravenous line in place throughout the procedure. Frequent blood pressure measurements should be taken, although clinically significant hypotension is very unusual when these simple precautions are taken.

Choice of radionuclide and ACE inhibitor. Since perturbations in renal physiology may alter the renal excretion of various radionuclides, it is important to briefly review the renal handling of the radionuclides that may be used in the captopril-stimulated renography. In contrast to conventional OIH, DTPA is excreted via the kidneys solely through glomerular filtration. Because of the superior imaging capabilities of ^{99m}Tc compared with ^{131}I labeling, the early phase of the [^{99m}Tc]DTPA study may also offer an index of renal perfusion and kidney size. Many investigators have preferred [^{99m}Tc]DTPA for captopril renography for these reasons.[38] On the other hand, the kidney handles OIH as it does paraamino hippurate (PAH), which is a marker for renal plasma flow. OIH is excreted by both glomerular filtration and tubular secretion, and it has a very high extraction ratio and excretion after its delivery to the kidney, which could be advantageous for renal imaging. Unfortunately, the ^{131}I label suffers from suboptimal imaging characteristics. More recently, [^{99m}Tc]MAG_3, which is excreted via the kidney in a fashion similar to PAH and OIH, has become clinically available for renography. Technetium-99m MAG_3 may become the radionuclide of choice because it offers both advanta-

geous technetium labeling characteristics and suitability for estimating renal plasma flow.

Although some investigators have reported good results with intravenous enalapril (0.04 mg/kg up to a maximum of 2.5 mg), which shortens the time of the test, most felt that oral captopril has given uniformly good results regardless of the dose used (25 or 50 mg). Further studies will be needed to validate whether even smaller doses of captopril will work or whether other ACE inhibitors should be used. Because a single dose of oral captopril has been remarkably free of serious side effects or toxicity when used for renography, the test appears to be safe even in patients with bilateral RAS. The authors did not feel that furosemide was needed to improve the accuracy of the test.

Analysis of the renogram. Once the appropriate patients have been selected for study and properly prepared for captopril renography, the remaining issue is how best to interpret the renogram. The issues include: Should the scintigraphic images or time-activity curves, or both, be analyzed? If the time-activity curves are used, should the scans be reported in a semiquantitative or semiqualitative fashion? Should only a postcaptopril study be done initially, or should a renogram without the ACE inhibitor challenge also be performed? If so, should the baseline study be done before the captopril renogram on the same day, or should it be done at another time?

The Working Party on Diagnostic Criteria of Renovascular Hypertension with Captopril Renography addressed each of these issues.[39] They felt that both the scintigraphic images, especially for the [^{99m}Tc]DTPA studies, and the computer-generated time-activity curves provide information about renal size, perfusion, and excretory capacity. Analysis of the time-activity curves provides considerably more information because there are three components to the curve, each of which can be helpful: the first is the time to maximal activity (T_{max}) and relative activity of each kidney, the second is the parenchymal transit time (PTT), and the third is the residual cortical activity (in actual counts) at 20 or 30 minutes compared with the counts at the peak activity. In addition, the time-activity curves of [^{99m}Tc]DTPA studies can be used to estimate the GFR of each kidney. In this fashion, the renogram provides a quantitative measure of comparative renal function and supplements the visual impression derived from the scintigraphic images.

The Working Party on Diagnostic Criteria of Renovascular Hypertension with Captopril Renography favored a semiquantitative grading system modified from that proposed by Geyskes[32] and Oei.[31,40] Even though the radiopharmaceuticals used in the earlier studies were primarily [^{99m}Tc]DTPA and [^{131}I]OIH, and the more recent studies were done with [^{99m}Tc]MAG_3, the renograms were generally similar, and the system proposed appears equally good.

They suggested the following grading system: grade 0, normal; grade 1, mild delay in upslope, maximal activity, T_{max} ($6 \leq T_{max} \leq 11$ minutes), or excretory phase; grade 2A, delay in upslope and T_{max} *with* evidence of an excretory phase; grade 2B, delay in upslope and T_{max} *without* evidence of an excretory phase; and grade 3, marked reduction or absence of uptake.
Examples of each of these grades have been published in the Working Party report and are depicted in Fig 5.

In addition, the committee recognized that the impact of captopril on the renogram could be an important way to select patients who have RVHT from those with anatomic RAS. They suggested that if the postcaptopril scan is grade 0 (normal), then the interpretation of the study should be that the patient has a low probability of having a hemodynamically significant renal artery lesion. The hallmark of functionally significant RAS appears to be change in the renogram, ie, deterioration of grade, following administration of ACE inhibition. (A change in grade may imply changes in more than one parameter of the renogram, eg, T_{max}, PTT, residual cortical activity, etc.) For example, if the baseline scan is grade 0 and the postcaptopril study is a higher grade, the renogram should be judged as showing a high probability that the patient has significant RAS. Grade 1 baseline scans that become grade 2A, 2B, or 3 are read as indicating a high probability that RAS is present. Grade 2A renograms at baseline that become grade 2B or 3 are also defined as high-probability scans. Of note, grade 2B or 3 studies may not worsen after captopril such that a lack of change may be indeterminant for the presence of RAS. Such changes in grade are pre-

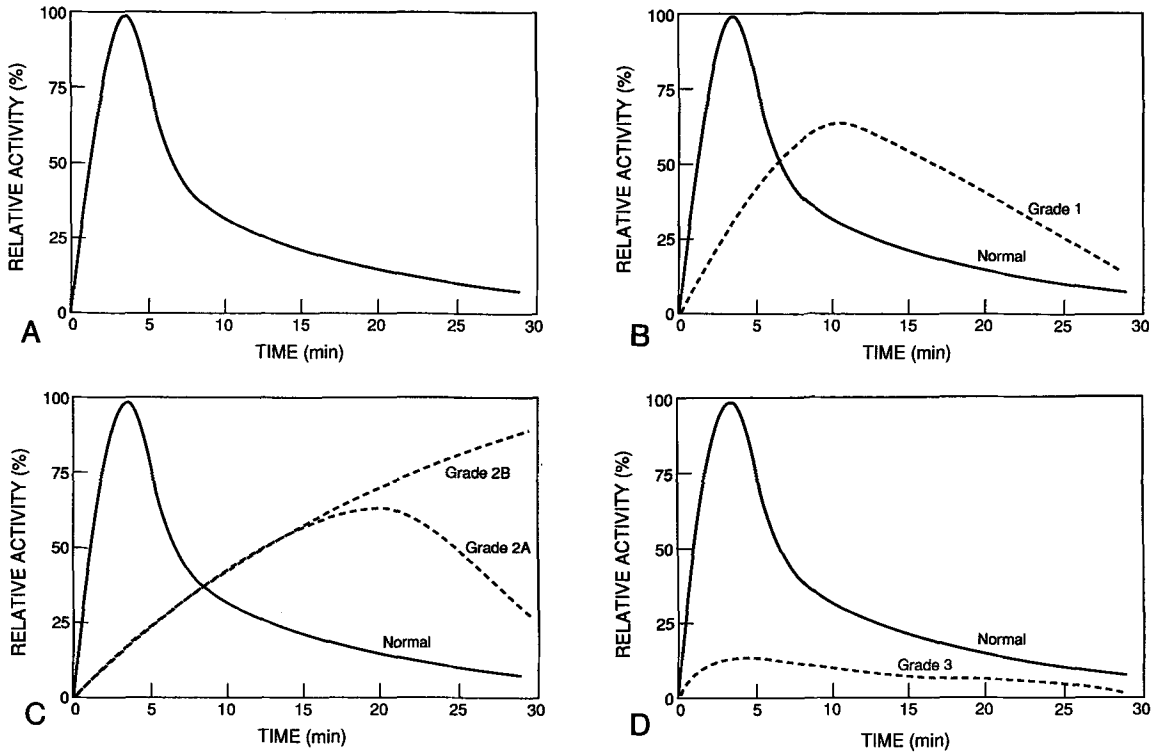

Fig 5. Proposed grading system for captopril renography. (A) Grade 0 (normal). (B) Grade 1. (C) Grades 2A and B. (D) Grade 3. See text for explanation.

sented in Table 2 and depict the putative degree of probability for the presence or absence of hemodynamically significant RAS. The Consensus Committee suggests that clinical investigators and nuclear medicine physicians report the results of captopril renography as high probability, indeterminant probability, or low probability based on the change in grade of the renogram before and after captopril.

Other investigators, particularly Chen et al,[41] Erbslöh-Moller et al,[37] and Mann et al,[42] have used quantitative measures—either time to peak activity, the GFR ratio between kidneys, or the residual cortical activity—to determine whether or not the renogram was normal. Chen et al studied 50 patients clinically likely to have RAS and then derived their criteria for an abnormal time-to-peak activity or abnormal GFR ratio, based on the findings in the group without renal artery lesions. They determined the mean plus two standard deviations for each of these parameters, and they designated the renogram as abnormal if either was greater than these confidence intervals. These criteria were then validated in another group of patients and found to be equally predictive.[19] Interestingly, in Chen's initial analysis using this quantitative paradigm, a GFR ratio of up to 1.5:1 (normal to affected kidney) was judged to be the normal range for these high-risk patients without RAS. Perhaps this wide confidence interval explains why the arbitrarily determined difference of 6% in GFR between kidneys used by Svetkey et al[22] reduced the diagnostic accuracy of captopril renography in their hands.

Table 2. Schematic of Renogram Grade Before and After Captopril Challenge

	Postcaptopril				
Baseline	Grade 0	Grade 1	Grade 2A	Grade 2B	Grade 3
Grade 0	L	H	H	H	H
Grade 1	L	I	H	H	H
Grade 2A	L	L	I	H	H
Grade 2B	L	L	L	I	H
Grade 3	L	L	L	I	I

Abbreviations: L, low probability of RAS; I, indeterminant probability of RAS; H, high probability of RAS.

Some have convincingly argued that baseline studies need not be done in patients with grade

0 (normal) renograms after captopril. This is based on the work of Fine et al,[23] which has shown that the postcaptopril study is virtually always normal in patients clinically unlikely to have RAS. Some centers still do both scans in all patients because of the inconvenience of making the patient return to the nuclear medicine department for a second study should the postcaptopril study be abnormal. However, there is a substantial additional cost in doing two renograms if only one is needed. Because of the diagnostic importance of the changes in the scan induced by an ACE inhibitor, the committee recommends that a baseline study should be done if the postcaptopril renogram is abnormal. Alternatively, the clinician may wish to forego the baseline renogram and proceed directly to renal angiography if the clinical index of suspicion for RVHT is high.

Captopril renography is a very promising diagnostic tool in the evaluation of the hypertensive patient. The data are sufficient to recommend this test as a useful, safe, and noninvasive way to diagnose RAS. It may also provide important information about the functional nature of the renal arterial lesion, and could potentially be useful in selecting patients for angiography when ischemic nephropathy is being considered as the etiology of renal failure in an individual patient.

However, concern exists that unless there is some standardization of the patients considered appropriate for study and of the methods for analyzing the test, the medical community will not be able to reproduce the results reviewed here, and this technique will also be abandoned. The possibility of safely and effectively finding the millions of individuals in the United States with RAS and significantly improving the outcome of their treatment makes it imperative that we use captopril renography in a careful and objective fashion. There is much to be gained if this procedure fulfills its promise.

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