Renal Scintigraphy in the Evaluation of Renovascular Hypertension: A Note of Optimism Yet Caution

In this issue of the *Journal*, Sfakianakis and colleagues (*1*) present provocative observations regarding the detection of renal artery stenosis (RAS) using captopril-stimulated radionuclide studies of the renovascular bed. Hypertension affects 50 million Americans and poses a tremendous health risk as hypertensive cardiovascular disease remains a leading cause of death in the 1980s. Because of the recent advances in percutaneous transluminal angioplasty and surgical techniques, there has been a renewed interest in developing a better screening test to identify the nearly 1 million Americans with potentially correctable renovascular hypertension (RVHT) (*2,3*). The reports of combining radionuclide studies of the kidney with angiotensin converting enzyme inhibition (CEI) offers promise and a sense of optimism in improving the noninvasive detection of significant stenosis of the renal arterial tree. However, a note of caution appears appropriate since several questions regarding the sensitivity and specificity of the combined technique remain. I will attempt to review the state of this work to date and pose questions for the future regarding the potential utility of this combined technique.

An historical perspective of renal scintigraphy suggests that a premature optimism for its diagnostic potential may have accompanied its development. Early overzealous expectations for iodine-131 (^{131}I) iodohippurate renography were never fully realized mainly due to a lack of specificity. This is believed by some to be one of the reasons that renal scintigraphy has been viewed by many clinicians to have limited usefulness in the evaluation of renal parenchymal disease and hypertension (*4*). During the Cooperative Study for Renovascular Hypertension, the [^{131}I]hippuran renogram was found to have a false-negative rate of 24% in the RVHT population as well as a false-positive rate of nearly 25% in the essential hypertension population (*5*). Additional studies documented a sensitivity and specificity of 80–85% such that the results of the [^{131}I]hippuran renogram approximate that of the conventional hypertensive intravenous pyelogram (IVP) (*6*). Later studies utilizing technetium-99m diethylenetriaminepentaacetic acid (DTPA) suggest that this radionuclide may offer better sensitivity in detecting patients with RVHT with preserved renal function (*7*). Nonetheless, it is imperative to recognize that the high prevalence of hypertension in the American population (~20%) coupled with the low incidence (<5% of hypertensives) of RVHT mandate that any screening test for RVHT will have a limited predictive value for identifying those patients with correctable RVHT unless it is highly specific (*8*).

In the various forms of renal artery stenosis, understanding the effect of CEI upon the kidney ipsilateral to the stenosis as well as the contralateral kidney is crucial in anticipating the putative changes in radionuclide studies of the kidneys after CEI. It appears that the RVHT is dependent upon renin secretion of the juxta-glomerular apparatus (JGA) from the underperfused, stenotic kidney and 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. CEI acts to interrupt the renin-angiotensin-aldosterone pathway by preventing the conversion of angiotensin I to angiotensin II such that both the vasoconstrictor/hemodynamic and aldosterone-stimulating effects of angiotensin II are blocked (*2*). In reviewing the effect of CEI in experimental models of two-kidney, one-clip (2K,1C) Goldblatt hypertension, Ploth (*9*) reported significant pressure-associated decreases in glomerular filtration rate (GFR), urine flow and salt excretion in the clipped kidney after CEI with SQ 20,881. It is postulated that studies to date regarding the decrease in GFR with CEI support the theory that maintenance of intrarenal resistance and GFR are mediated by Angiotensin II-dependent, efferent arteriolar constriction when renal perfusion pressure is diminished, as seen with preglomerular stenosis (*10*). It is also widely recognized that the effects of CEI are not

confined to the ipsilateral kidney. Despite the reduction in arterial pressure, the nonclipped contralateral kidney exhibits dramatic increases in GFR, urine flow and salt excretion which suggests contralateral renal vasodilatation (*9*). In a related series of experiments, CEI did indeed reduce arterial pressure and renal blood flow of the clipped kidney, yet renal blood flow of the unclipped kidney increased significantly (*11*). In our canine model of 2K,1C hypertension, CEI with captopril did not further reduce renal plasma flow of the clipped kidney while effective renal plasma flow (ERPF) of the unclipped contralateral kidney rose by 22% despite a 20% decrease in arterial pressure (*12*). Overall, CEI in experimental models of unilateral renal artery stenosis demonstrates a reduction in mean arterial pressure associated with a diminution of function of the stenotic kidney while the contralateral kidney exhibits enhanced renal hemodynamics and excretory function. These expected physiological changes of the stenotic and contralateral kidney after CEI are the basis of the asymmetry of renal function detected by renal scintigraphy which should help improve the noninvasive diagnosis of unilateral RAS. With bilateral RAS, detection of stenosis may become more complicated for two reasons: First, the exaggerated degree of asymmetry of renal function in response to the challenge of CEI may be greatly diminished since both kidneys behave in a "clipped" fashion. Second, pre-existing renal insufficiency secondary to advanced renovascular disease may compromise the ability of some radionuclide such as [^{99m}Tc]DTPA to assess accurately the changes in renal function.

In a solitary kidney with stenosis, the issue of degree of renin dependency of the hypertension remains controversial. The effect of CEI upon systemic arterial pressure as well as renal function and hemodynamics are also a matter of debate. Traditionally, the 1-kidney, 1-clip (1K, 1C) model has been thought to be a volume-dependent (low renin) form of hypertension rather than a renin-dependent form. In our sodium-replete canine model of 1K, 1C hypertension, CEI with captopril reduced mean arterial pressure but did not significantly alter GFR, renal plasma flow, nor [^{99m}Tc]DTPA or [^{131}I]hippuran renography (*13*). In contrast, Lee and Blaufox (*14*) report a significant decrease in GFR in response to CEI in their rat model of 1K, 1C hypertension. The response to CEI may be a function of the degree and duration of RAS as well as the state of sodium balance (*13*). The state of sodium balance may play a pivotal role in the activation of the renin-angiotensin system regarding the maintenance of mean arterial pressure and renal function in this model. Significant sodium depletion, induced by either low salt diet or diuretics, may be responsible for stimulation of the renin angiotensin system such that both arterial pressure and renal function become Angiotensin II-dependent—whether there is renal artery stenosis leading to that kidney or not. These types of physiological considerations are particularly important in designing clinical protocols and scrutinizing data generated from captopril-stimulated renography.

Equipped with an understanding of the effects of CEI upon renal physiology in various forms of RAS, one can then attempt to put into perspective the clinical observations regarding CEI-stimulated renography reported in recent years. Majd and colleagues (*16*) first reported that captopril altered the [^{99m}Tc]DTPA renograms in four hypertensive children suspected of having renal artery stenosis. Since that time, many other preliminary reports have been issued. Early publications from the Netherlands (*17*) and the U.S. (*18*) examined the effect of CEI with captopril or enalapril upon individual kidney function using radionuclide techniques in patients with RAS. The study of Wenting et al. (*17*) in patients with unilateral renal artery stenosis or essential hypertension is of particular interest. Changes in ERPF and GFR (as measured by [^{131}I]hippuran and [^{125}I]thalamate clearances, respectively) in response to captopril (50 mg. p.o.) were studied in 14 patients with unilateral RAS and normal renal function who had their antihypertensive medications withheld for two weeks prior to study. In addition, single kidney extraction ratios for [^{131}I]hippuran and [^{125}I]thalamate from blood samples obtained from the aorta and renal veins were analyzed before and after captopril. The renal extraction ratios for both [^{131}I]hippuran and [^{125}I]thalamate were greatly reduced on the stenotic side after captopril in seven of 14 patients, with less pronounced (yet significant) changes in the extraction ratios of the stenotic kidneys of the other seven patients with unilateral RAS. Total and ipsilateral GFR was reduced but total ERPF (as measured by [^{131}I]hippuran clearances) did not fall. The findings of an unchanged clearance of sodium iodo-hippurate coupled with a reduction in the extraction ratios suggests that renal blood

flow may have increased in response to captopril (*17*). Interestingly, the patients with the greatly reduced single kidney extraction ratios following CEI had rises in serum creatinine during long-term captopril therapy. Subsequent [^{99m}Tc]DTPA uptake was absent on the stenotic side in these patients maintained on captopril 150 mg daily for 3–5 wk. Both the loss of renal function and the changes in the [^{99m}Tc]DTPA renograms were reversible after captopril was discontinued.

The studies of Wenting et al. (*17*) are important to our understanding of the response to CEI in patients with RVHT for two reasons. First, the findings document that captopril may change the renal handling of conventional radionuclides used for renal scintigraphy without necessarily reflecting the accurate hemodynamic and functional changes within the kidney. This may be especially noteworthy to help reconcile changes seen in the [^{131}I]hippuran renogram of the stenotic kidney with reports of less pronounced changes in renal blood flow in that kidney when it is measured by alternative clearance techniques. As pointed out by Sfakianakis et al. (*1*), the "cortical retention" of the stenotic kidney may be more a function of diminished urine flow rate within the cortical nephrons in response to CEI rather than a reduction in ipsilateral ERPF. Second, these studies are important because they emphasize the value of quantitating individual kidney function in patients with RVHT in response to CEI agents or other medical therapies. It must be recognized that total renal function (as assessed by serum creatinine or other total GFR measurements) may change little in response to CEI. However, the absence of change of total GFR in unilateral RAS may actually reflect a substantial detrimental reduction of GFR of the stenotic kidney with a compensatory increase in GFR of the contralateral kidney. Indeed, more recent reports from Japan (*19*) and Australia (*20*) utilizing computer-assisted [^{99m}Tc]DTPA renography to follow patients with RVHT on chronic captopril therapy documented significant reductions in GFR of the stenotic kidney(s).

Application of this combined technique for use in screening hypertensive patients was introduced by Oei, Geyskes, and colleagues from the Netherlands (*21*). In this report and a subsequent publication (*22*), these investigators studied a series of patients with unilateral RAS with [^{99m}Tc]DTPA and ^{131}I hippuran renography before and after captopril (25 mg p.o.) at the time of diagnosis and then subsequently after correction of RAS with percutaneous angioplasty (PTA). They concluded that (*22*) "therapy with captopril before PTA caused an impressive deterioration of the hippuran and, even more so, in the DTPA renogram, in six patients whose hypertension was cured (*5*) or improved (*1*) after PTA or nephrectomy." These changes with captopril were not seen in three of four patients with normal angiography. Additional reports of small series of hypertensive patients evaluated with captopril renography were recently presented at the Society of Nuclear Medicine meeting in Toronto (*23–26*).

Before endorsing widespread application of this combined technique for screening and detection of RAS, several observations regarding screening techniques must be reviewed. We must recognize that our overall objective is to identify those patients with potentially correctable RVHT from a vast number of hypertensive patients. Having recognized the RVHT patients, the goals of therapy are to improve blood pressure control and preserve renal function. A long-term study from the Mayo Clinic suggests that these goals may be better met with interventional therapy as RVHT patients treated surgically appear to have less morbidity and mortality compared to those treated medically (*27*). To identify these patients whom we hope to benefit, we must recognize that the predictive value of any screening test for RVHT may be limited by the high prevalence of hypertension in our population coupled with the relatively low incidence (<5%) of RVHT (*4*). For example, let's assume we use a good screening test with 90% sensitivity and specificity to screen a hypertensive population of 1,000 patients with an expected RVHT rate of 5% [i.e., 50 RVHT patients and 950 essential hypertension patients (EHT)]. Of the 50 RVHT patients, there would be 45 patients (0.9×50) with a positive screening test and five patients with a false-negative study. Of the 950 EHT patients, 855 (0.9×950) would be negative, yet 95 patients would have a false-positive study. Overall, more than twice the number with a positive screening test (95 versus 45) would actually have EHT such that only 33% of the positive screening test would have been predictive of RVHT. A significant number of patients with false-positive results may then require additional costly and invasive procedures to make a definitive diagnosis. To

define proper levels of sensitivity and specificity of this combined technique, the patient population should be referred because of the clinical suspicion of RVHT and then be enrolled in a consecutive, prospective fashion. Results of the baseline and captopril-stimulated renography must be interpreted in a blinded fashion without knowledge of angiographic findings. Using these precautions, it appears dubious that a 100% sensitivity and specificity for RVHT will ever be attained. Nonetheless, captopril-stimulated renography appears to be an advancement towards our goal of noninvasively detecting potentially correctable RVHT.

Relevant questions remain regarding the standardization and implementation of the combined technique in the clinical setting, as well as its overall utility in various forms of RVHT. The combined technique clearly appears to increase the sensitivity of both [^{99m}Tc]-DTPA and [^{131}I]hippuran renography in patients with unilateral renal artery stenosis and preserved renal function (*1,22*). Will captopril renography improve our ability to predict the success of revascularization or angioplasty of a kidney better than existing studies? Further study is also needed in patients with bilateral renal artery stenosis. Appropriate concern exists in this patient population whether (a) CEI agents employed at the time of radionuclide studies could result in transient renal insufficiency if stenoses are severe, volume status is suboptimal, and/or the dosage of the CEI agent is excessive, or (b) whether preexisting renal insufficiency will limit the efficacy of radionuclides such as [^{99m}Tc]DTPA which are excreted via GFR alone. The utility of a radionuclide like [^{131}I]hippuran which is excreted by both tubular secretion and GFR may be preferable in this circumstance and be the agent of choice when mild to moderate renal insufficiency exists. The efficacy of single-dose captopril renography in patients with RAS of a solitary kidney or stenosis of a renal transplant graft is also not certain. In the hypertension renal transplant patient, Dubovsky et al. (*24*) have reported that three days of captopril administration prior to [^{131}I]hippuran renography reduces ERPF of the transplanted kidney and distinguishes RAS from other causes of posttransplant hypertension. More extensive observations in this patient population with a solitary kidney are obviously warranted. Finally, a larger number of observations is also required to determine if there is increased specificity of captopril renography in the essential hypertensive population. Hopefully the combination of CEI and radionuclide studies may be able to lessen the need for invasive angiography with its attendant risk of allergic reaction or potential nephrotoxicity, and afford a more cost-effective method of evaluating a selected group of hypertensive patients.

Pursuit of these questions has led to the recent establishment of an international, multicenter study to evaluate more completely captopril renography in the hypertensive population.* The situation demands a thoughtful scientific approach to designing clinical protocols, patient selection, and long-term follow-up regarding blood pressure control and preservation of renal function. This effort deserves ongoing peer review and quality control assessment to guarantee adequate evaluation of captopril renography. Further in-depth study is required before widespread application of the combined technique can be enthusiastically advocated. Otherwise, we may be destined to repeat the past in which lack of specificity led to lack of creditability.

REFERENCES

1. Sfakianakis GN, Bourgoignie JJ, Jaffe D, et al. Single dose captopril scintigraphy in the diagnosis of renovascular hypertension. *J Nucl Med* 1987; 28:1383–1392.
2. Dzau V, Gibbons G, Levin D. Renovascular hypertension: an update on pathophysiology, diagnosis and treatment. *Am J Nephrol* 1983; 3:172–184.
3. Novick A, Straffon R, Stewart B, et al. Diminished operative morbidity and mortality in renal revascularization. *JAMA* 1981; 246:749–753.
4. Fine EJ, Scharf SC, Blaufox MD. The role of nuclear medicine in evaluating the hypertensive patient. In: Freeman L, Weissmann H, eds. *Nuclear Medicine Annual.* New York: Raven Press, 1984:23–79.
5. Maxwell M. Cooperative study of renovascular hypertension: current status. *Kidney Int* 1975; 8 (suppl):153–160.
6. Harvey RJ, Krumlovsky F, delGreco F, et al. Screening for renovascular hypertension. *JAMA* 1985; 254:388–393.
7. Chiarini C, Esposti ED, Lusinno F, et al. Renal scintigraphy versus renal vein renin activity for identifying and treating renovascular hypertension. *Nephron* 1983; 32:8–13.

8. Arlat I, Rosenthal J, Adam WE, et al. Predictive value of radionuclide methods in the diagnosis of unilateral renovascular hypertension. *Cardiovasc Radiol* 1979; 2:115–25.
9. Ploth D. Angiotensin-dependent mechanisms in two-kidney, one-clip renal vascular hypertension. *Am J Physiol* 1983; 245:F131–F141.
10. Blythe W. Captopril and renal autoregulation. *N Engl J Med* 1983; 308:390–391.
11. Huang WC, Navar LG. Effects of unclipping and converting enzyme inhibition bilateral renal function in Goldblatt hypertensive rats. *Kidney Int* 1983; 23:816–822.
12. Nally JV, Clarke HS, Grecos GP, et al. Effect of captopril on 99Tc-Diethylenetriamine pentaacetic acid renograms in two-kidney, one clip hypertension. *Hypertension* 1986; 8:685–693.
13. Nally JV, Clarke HS, Gupta BK, et al. Captopril renography in two-kidney and one-kidney Goldblatt hypertension. *J Nucl Med* 1987; 28:1171–1179.
14. Lee H, Blaufox MD. Differential effect of captopril on GFR in rats with renovascular hypertension [Abstract]. *J Nucl Med* 1985; 26:P72.
15. Curtis J, Luke R, Whelchel J, et al. Inhibition of angiotensin-converting enzyme in renal-transplant recipients with hypertension. *N Engl J Med* 1983; 308:377–381.
16. Majd M, Potter BM, Guzzetto PC, et al. Effect of captopril on efficacy of renal scintigraphy in detection of renal artery stenosis [Abstract]. *J Nucl Med* 1983; 24:P23.
17. Wenting GJ, Tan-Tjiong HL, Derkx FHM, et al. Split renal function after captopril in unilateral renal artery stenosis. *BMJ* 1984; 288:886–890.
18. Bender W, LaFrance N, Walker WG, et al. Mechanism of deterioration in renal function in patients with renovascular hypertension treated by enalapril. *Hypertension* 1984; 6:I193–I197.
19. Miyamori I, Yasuhara S, Takeda Y, et al. Effects of converting enzyme inhibition on split renal function in renovascular hypertension. *Hypertension* 1986; 8:415–421.
20. Jackson B, McGrath BP, Matthews PG, et al. Differential renal function during angiotensin converting enzyme inhibition in renovascular hypertension. *Hypertension* 1986; 8:650–654.
21. Oei H, Geyskes G, Dorhout M, et al. Captopril induced renographic alteration in unilateral renal artery stenosis [Abstract]. *J Nucl Med* 1984; 25:P5–6.
22. Geyskes GG, Oei HY, Faber JAJ. Renography: prediction of blood pressure after dilatation of renal artery stenosis. *Nephron* 1986; (suppl 1):54–59.
23. Hilson A, Frankel AH, Othman S, et al. Captopril enhanced ^{99m}Tc-DTPA studies as a screening test for renovascular disease in the setting of the general Nephrology Clinic [Abstract]. *J Nucl Med* 1987; 28(suppl): 613.
24. Sfakianakis GN, Bourgoigne JJ, Jaffe D, et al. The effect of captopril on renography in renovascular hypertension (RVH): a predictor of response to angioplasty [Abstract]. *J Nucl Med* 1987; 28:613.
25. Fommei E, Ghione S, Palla L, et al. The scintigraphic captopril test in renovascular hypertension [Abstract]. *J Nucl Med* 1987; 28:613.
26. Subramanian K, Sarker S, Mann S, et al. Single dose captopril renography with Tc-99m-DTPA and I-31-hippuran in renovascular hypertension (RVH) [Abstract]. *J Nucl Med* 1987; 28:735.
27. Hunt JC, Strong CG, Sheps SG, et al. Diagnosis and management of renovascular hypertension. *Am J Cardiol* 1969; 23:434–445.
28. Dubovsky E, Curtis J, Luke R, et al. Effect of captopril on ERPF in differential diagnosis of hypertension in renal transplant recipients [Abstract]. *J Nucl Med* 1985; 26:P73.

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