Scintigraphic Evaluation of Renovascular Hypertension

Hee-Myung Park and Heun Young Yune

Key Words: Renovascular hypertension, hypertension, scintigraph

Only less than 10% of patients with hypertension have curable causes, of which renovascular hypertension (RVH) is the most common. Since the renal artery stenosis (RAS) is the usual culprit and its correction requires a costly interventional procedure such as renal artery bypass or intraluminal angioplasty, there is a great need for non-invasive screening tests to select patients who will benefit most from these procedures.

The pathophysiology of renovascular hypertension:

In his classic experiments on dogs, Goldblatt et al. (1934) were able to induce acute and chronic hypertension by applying partial ligatures about renal arteries. It was the first experiment to show that ischemic kidney caused hypertension. This was later found to be renin-mediated. The decrease of arteriolar perfusion pressure and resulting diminution in the afferent arteriolar stretch triggers renal arterial baroreceptors to signal the juxtaglomerular cells to produce more renin. Renin, in turn, converts angiotensinogen, an hepatic protein, to form angiotensin I, which is biologically inactive. Angiotensin I is converted to angiotensin II by the function of angiotensin converting enzyme (ACE), primarily located in the endothelium of pulmonary vasculature. Angiotensin II is a potent vasoconstrictor and also stimulates the adrenal secretion of aldosterone which promotes re-absorption of sodium at the level of the distal convoluted tubule. In short, ischemia of the kidney causes increased renin production followed by increased angiotensin II and hypertension.

RAS versus RVH

Identification of renal artery artery stenosis is not equal to the diagnosis of renovascular hypertension. Renal artery stenosis is the most common cause of renal ischemia which is necessary to cause renovascular hypertension. However, renovascular hypertension is not necessarily the result of renal artery stenosis. Indeed, renal artery stenosis can be the result of hypertension itself. It is known that there is an accelerated atherosclerosis in patients with hypertension and this process may include renal artery. Also, renovascular disease can be found in 32% to 48% of the normotensive elderly with atherosclerosis (Eyster et al. 1962; Kehlgy et al. 1964).

The two major causes of renal artery stenosis are atherosclerotic vascular disease involving the renal artery and fibromuscular dysplasia. Atheromatous disease of the renal artery accounts for approximately two-thirds of all causes of renovascular hypertension. This occurs more frequently in men than women with two to one ratio, and typically occurs in patients beyond the age of fifty. Atheromatous plaques are usually found in the proximal one-third of the renal arteries and is often bilateral, but may be more severe on one side. Fibromuscular hyperplasia on the other hand, occurs most commonly in females younger than 40 years of age. The most common type of dysplasia is medial fibromuscular dysplasia which is characterized by a string of "beads" in the distal main renal artery on angiography, and is
often bilateral. Other causes of renal artery stenosis include renal artery dissection, thrombosis, embolism, aneurysm, A-V malformation, arteritis and coarctation of abdominal aorta. Also, an extrinsic pressure to the renal artery by local tumors, cyst, abscess or some abnormality of the great vessels can cause decreased renal perfusion. Non-arterial causes for decreased renal perfusion include renal vein thrombosis, severe parenchymal renal disease, severe obstructive uropathy and compression of the kidney (Page kidney) due to hematoma or perinephric abscess (McAfee et al. 1977).

Renal artery stenosis is identified by techniques based on morphological assessment of renal artery anatomy, such as conventional or digital arteriography, Doppler sonography with flowmetry, spiral CT angiography with contrast and magnetic resonance angiography.

The ultimate proof of RVH is cure of hypertension following alleviation of renal artery stenosis. Since it requires a costly interventional procedure such as renal artery bypass or intraluminal angioplasty, there is a great need for a non-invasive diagnostic test to select patients who will benefit most from these procedures. The diagnosis of RVH requires studies capable of detecting or unmasking renin overproduction due to renal artery stenosis or demonstrating deterioration of the function of the affected kidney following abolishment of the renin effect. Renal vein renin ratio and Captopril stimulated renin level by selective renal vein catheterization proved to be highly specific, but low in sensitivity and accuracy, and require an invasive procedure. Non-invasive tests such as rapid sequence excretory urography, intravenous digital subtraction angiography, Doppler-ultrasonography and peripheral blood renin level are neither specific nor sensitive in the diagnosis of RVH. The ACE inhibitor challenged renal scintigraphy, a noninvasive procedure, is a promising diagnostic test, and will be discussed further.

Effect of ACE inhibitor drugs

ACE inhibitors lower blood pressure through a complex mechanism which may include increase in bradykinin and vasodilator prostaglandin in circulating blood in addition to reduction in angiotensin II (Williams, 1988). Currently available ACE inhibitor drugs are: Captopril(Capoten, Capozide), Enalapril(Vasotec Tablet and IV form) and Lisinopril (Zestril, Zestoretic, Prinivil, Prinzide). The use of these drugs for patients with renovascular hypertension may adversely affect the ischemic kidney, and the renal function may deteriorate.

In patients with renovascular hypertension, because of the lowered pressure in the afferent arterioles, the glomerular filtration pressure in decreased causing reduction in the glomerular filtration rate (GFR). However, because of a renin-mediated increase in angiotensin II level, vasoconstriction particularly of the efferent arterioles follows. This helps to maintain the perfusion pressure of the glomeruli. Administration of an ACE inhibitor to such patients will abolish the angiotensin II induced vasoconstriction of the efferent arterioles and inadvertently lowers the glomerular filtration pressure and GFR. From the standpoint of the affected kidney, it may be said that the ACE inhibitor “adds insult to injury”. ACE inhibitor challenged renal scintigraphy takes advantage of this adverse effect, in that the exaggerated difference between the normally functioning kidney and worsening of the affected kidney can easily be detected.

ACE INHIBITOR RENOGRAPHY

In 1983, Maji et al. observed unilateral deterioration of renal function in several hypertensive children following normalization of blood pressure by Captopril and suggested that Captopril may be used to enhance the efficacy of renal scanning for detection of renal artery stenosis. Captopril has been the most widely used ACE inhibitor in conjunction with renal scintigraphy since. This is, however, an oral agent and the absorption from the gastrointestinal system is not necessarily prompt or uniform in every patient, and there is no consensus among investigators as to the proper amount of Captopril to be used e.g. 25 mg or 50 mg. Some advocate crushing the tablet to improve the gastric absorption and some do not.

The sensitivity and specificity of Captopril-challenged renal scintigraphy using Tc99m-DTPA in hypertensive patients have been reported to be 91 to 94% and 93 to 97% respectively (Dondi et al. 1989; Chen et al. 1990;
Mann et al. (1991). Dondi et al. (1992) showed a positive and negative predictive values of 97% and 72% respectively in 51 patients who had renal artery revascularization procedures. In his study, 32 patients out of 33 who had a positive Captopril renal scintigraphy showed improvement of cure of hypertension after renal artery dilatation procedure and 13 out of 18 patients who had a negative Captopril renal scintigraphy showed no improvement after the procedure.

Clinical indications for ACE inhibitor renography

To make it most cost effective, ACE inhibitor renography should be used in patients with a high clinical index of suspicion, i.e., with signs and symptoms suggesting renovascular hypertension (Working group, 1987).

1. Sign of atherosclerotic or other arterial stenosis: systolic/diastolic epigastric, subcostal, or flank bruit.
2. Evidence of generalized vascular disease: peripheral or cerebral vascular disease, aortic aneurysm or occlusive disease and coronary heart disease.
3. Unilateral small kidney discovered by any clinical study.
4. Worsening of hypertension and unexplained impairment of renal function.
5. Impaired renal function following ACE inhibitor therapy.
6. Accelerated or malignant hypertension.
7. Hypertension refractory to multiple drug regimen.

Radionuclides for ACE inhibitor renography

The radionuclides that have been used for ACE inhibitor renography are I-131- or I-123-orthiodohypurate, Tc99m-DTPA and more recently Tc99mMAG3 (mercaptoacetyl triglycine). Tc99m has much better photon characteristics than I-131 or I-123. Iodine-123 is expensive and not readily available. Tc99mDTPA is a glomerular agent and has a much bigger distribution volume than Tc99mMAG3, thus more background activity. Tc99mMAG3 is a tubular agent, and is extracted by the tubular cells and excreted into the tubular lumen. For the clearance of this agent from the renal cortex, it requires urine flow through the tubular lumen. In other words, cortical clearance of this agent depends on the renal function. Tc99mMAG3 renal images are superior to Tc99mDTPA images due to the greater renal uptake and lower background activity. For these reasons, Tc99mMAG3 is being accepted as a better renal imaging agent than Tc99mDTPA or I-131 OIH.

A single visit ACE inhibitor renography protocol

Although the Captopril renography has been used most widely, it usually takes two days to complete since a baseline study is needed for comparison when the Captopril challenged study is abnormal. This is usually done the next day to allow time for the background radioactivity to clear. Recently, enalaprilat (Vasotec IV) became available and is being used as an effective ACE inhibitor. Enalaprilat (Vasotec LV) is the active metabolite of the oral agent Enalapril maleate (Vasotec tablets). The usual dosage for clinical use is 1.25 mg IV given slowly over five minutes four times a day. Adverse reactions are rare: hypertension in 3.4%, headache in 2.9% and nausea in 1.1% of patients have been reported. For ACE-inhibitor renography, Vasotec has advantage over Captopril. Because of it is given intravenously, the effect is faster and reliable than with the Captopril tablet. When used in conjunction with Tc99mMAG3, it is possible to complete a baseline study and ACE inhibitor study in one visit (Sfakianakis et al. 1991). This can be done in one hour and is accepted well by outpatients.

Single visit ACE-inhibitor renography

Patient preparation:
1. Normal breakfast with an extra fluid intake. If the patient is on an ACE inhibitor, and/or a diuretic, withhold the morning dose. The patient will receive Vasotec and Lasix as part of the study.
2. Gamma camera and computer: to be set up for 25 minutes data acquisition at a rate of 30 seconds per frame and one image per 60 seconds.
3. Oral fluid intake before the study: water or soft drink, an entire 12 oz can (10 ml/kg).
4. Empty bladder.
5. Start I.V. with an angiocath and 3 3-way stopcock. Keep the I.V. open with 500 ml normal saline (12 drops per minute). Patient is positioned supine over a gamma camera for a pos-
Imaging protocol (refer to Figure 1)

1. When the patient is prepared as above, check the blood pressure, and inject Tc99mMAG3 1 mCi, and start a baseline 25 min renal scintigraphy.

2. After the baseline study, let the patient empty bladder, and rehydrate the patient with the same amount of liquid. Reposition the patient, and check blood pressure.

3. Inject Enalaprilat I.V. slowly over 5 minutes. The dose is 0.04 mg/kg diluted in 10 ml of saline. Wait 10 minutes, and check the blood pressure.

4. Inject 9.0 mCi of Tc99mMAG3 I.V., and start the second renal scintigraphy.

5. Three minutes into the second study, administer Lasix 20 mg I.V.

The pediatric dose of Tc99mMAG3 is 150 μCi per kg in total, that is 10% of which should be used for the first part of the study (baseline study) and 90% of the dose to be used as inhibitor study. Lasix is used to reduce the possibility of urinary retention in the calyces which may inadvertently be included in the cortical region of interest. Foley catheter should be inserted if the patient had a recent renal renal transplantation, known vesicoureteral reflux, or a partial bladder outlet obstruction. During the study, if the blood pressure drops too low, and is less than 30% of the baseline, sodium chloride infusion may be increased.

Interpretation of ACE inhibitor-Tc99mMAG3 study

Delayed cortical clearance from, or non-visualization of a portion of an entire kidney, and a rising renogram curve relative to the baseline study are the abnormal finding. Although a baseline study alone may often be enough to identify the compromised kidney, it is necessary to demonstrate worsening of the renal function following an ACE inhibitor for the diagnosis of RVH. Visual estimation and comparison of the rates of cortical clearance on the images obtained before and after an ACE inhibitor are very important. One, however, should not blindly accept the images without the renograms and vise versa. Exposing the film with a reasonably good gray scale is important since too dark or too light images may cause an error in interpretation.

Quantification of scintigraphic abnormality is desirable, but there is no universally accepted protocol. There are several unresolved technical questions on quantification of the ACE inhibitor renogram including ideal time segment per frame, degree of smoothing the curve, and background subtraction technique e.g. a complete ring surrounding the kidney, half ring on the lateral aspect of the kidney or half ring below the kidney, etc. The most critical problem arises from the difficulty of isolating renal cortex from calyces when drawing a region of
interest over the cortex. This may happen even after the Lasix is administered if the urine flow is limited. In a normal kidney, renal cortical activity at 20 minutes (% RCA-20) is less than 30% of the maximum (Sfakianakis et al. 1991) (Fig. 2).

\[
\text{%RCA-20} = \frac{(30 \text{ sec cortex - bkg}) \times 100}{(30 \text{ sec cortex - bkg}) \text{ at peak}}
\]

An increase in renal cortical activity by 10% following ACE inhibitor with an absolute value in excess of 30% represents a positive test for renovascular hypertension. In patients with renal dysfunction the baseline renal cortical activity is usually greater than 30%. A further increase by more than 10% following ACE inhibitor is considered a positive test. In patients with a very poor renal function, ACE inhibitor scintigraphy showing no discernible changes indicate parenchymal renal disease. Sfakianakis (Sfakicarmakis et al. 1993) compared Vasotec scintigraphy and angiography, and found three patterns: 1. When the degree of renal artery stenosis is 60 to 95%, Vasotec study showed an increase in RCA more than or equal to 10 percentage points above the baseline. Prognosis was favorable for a cure of hypertension in these cases. 2. When the degree of stenosis is 95 to 100% but with abundant collaterals, there was no change in the renogram curves before and after ACE inhibitor, and showed a small hypofunctioning kidney. The prognosis after renovascular dilatation or graft surgery was favorable for improved renal function, but less favorable for cure of hypertension. 3. When the degree of stenosis is 100% with few collateral vessels, the baseline scan showed atrophic and non-functioning kidney and Vasotec study
showed no change in the renogram curve which was only mimicking the background activity.

It is important to confirm the ACE inhibitor scintigraphy findings with one of the morphologic studies of the renal artery. Renal angiography is probably the most useful for the purpose, and is necessary prior to attempted correction of the stenosis for better anatomic localization of the stenosis and overall evaluation of the vascular anatomy of the abdominal aorta and its tributaries.

Illustrative cases

Case 1: A 59 year old female with history of hypertension and myocardial infarction was found to have an abdominal aortic aneurysm with bilateral renal artery stenosis (Fig. 3-1). An aortic bypass graft and one renal artery saphenous vein graft were planned. The clinical question was whether she had a RVH and if so which side was responsible. The side with a more hemodynamically significant lesion were to be repaired first to minimize the risk of losing total renal function.

A baseline renal scintigraphy showed a fairly good perfusion and function bilaterally with a normal renogram curve (Fig. 3-2). The baseline renogram of the left kidney was also normal (not shown). The Vasotec-challenged renal scintigraphy, however, revealed a marked retention of the radioactivity in the right renal cortex (Fig. 3-3) indicating that the patient indeed had a renovascular hypertension and the right kidney was responsible. The right renal artery stenosis was repaired and the blood pressure was normalized. A postoperative follow-up scan revealed a good cortical clearance and a normalized renogram curve (Fig. 3-4).

Case 2: A 49 year old female was admitted to the hospital complaining of severe headaches. Evaluation for subarachnoid hemorrhage was negative. The blood pressure was 190/110. There was no previous history of hypertension. Epigastric bruit was present. An ACE inhibitor renal scintigraphy was performed to rule out renovascular hypertension.

The baseline study using 1 mCi of Tc99m-MAG3 (Fig. 4-1) revealed a good perfusion to
Fig. 3-3. Vasotec-challenged renal scintigraphy using 9 mCi of Tc99m-MAG3 showing a marked retention of the activity in the cortex of the right kidney. Only five one minute images with time interval as in Fig 2 are presented. No apparent radioactivity is seen in the right renal pelvis indicating a marked reduction in function. This finding is confirmed by the rising renogram curve.

Fig. 3-4. Another renal scintigraphy was obtained after the right renal artery stenosis was surgically repaired and her blood pressure returned to normal. The post-Vasotec study showed that the right renal cortex cleared the activity normally as the left one and the renogram was also normalized. (The case was kindly provided by Dr. Donald Schauwecker)
both kidneys. The left kidney showed a normal function with a rapid cortical clearance. The right kidney showed a prolonged cortical activity with a minimal activity appearing in the renal pelvis much later than the left side. The second study using 9mCi of Tc99mMAG3 after 2.4 mg of Vasotec I.V. showed again a normal left kidney and a marked retention of cortical activity on the right with no apparent tracer activity appearing in the renal pelvis (Fig. 4-2). This findings suggested that she had a RVH and the right kidney was responsible. Subsequently obtained renal arteriogram (Fig. 4-3) showed bilateral 80 to 90% ostial stenosis. The right renal artery stenosis was associated with a 90 mmHg systolic gradient and the left side, a 65 mmHg gradient. The left kidney had an accessory renal artery, which apparently helped the left kidney to maintain a functionally normal perfusion.

**The Diagnostic pitfalls**

In addition to the few technical factors discussed earlier, a variety of conditions can lead into a false diagnosis. For instance, a full bladder delays emptying of the collecting system, which may make the study difficult to interpret. A low output heart failure and profound hypotension cause renal ischemia and oliguria. These conditions may result in a false positive renal scintigraphy. Renal parenchymal diseases e.g. acute tubular necrosis, nephrotoxic drugs,
Renovascular Hypertension

**Fig. 4-2.** A Vasotec challenged renal scintigraphy using 9 mCi of Tc99m MAG3 showing a marked cortical retention on the right. The right renal pelvis (arrow) appears to be free of any radioactive urine. These findings proved that there was a worsening of the function of the right kidney following the administration of the ACE inhibitor. This finding indicated the right kidney was responsible for the hypertension.

**Fig. 4-3.** A digital abdominal aortogram demonstrated two renal arteries on the left. The accessory renal artery (arrow) originated a short distance above the main. There is a single renal artery on the right (arrow head). All three were stenotic at or just beyond their origin. The right renal artery stenosis was associated with a greater systolic gradient (90 mmHg) than the left main (65 mmHg).
glomerulonephritis, obstructive uropathy, renal vein thrombosis should be ruled out before the test (Sfakianakis et al.).

Summary

ACE inhibitor challenged renal scintigraphic studies offer noninvasive means of evaluating patients for renovascular hypertension, and provide help in selecting patients who will benefit most from interventional procedures designed for alleviation of renal artery stenosis. These studies provide functional assessment of each kidney which also helps the vascular surgeons to plan which renal artery to repair first, when bilateral renal arteries are stenotic, prior to an abdominal aortic aneurysm repair. Vasotec challenged Tc99mMAG3 renal scintigraphy is one of such tests with several advantages over other similar methods, and appears to have a great potential of being a preferred scintigraphic study for evaluation of renovascular hypertension.

REFERENCES


