Renovascular Hypertension: A Noninvasive Screening Approach Using Captopril Renography

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Background: Noninvasive cost-effective screening of hypertensive patients for renovascular hypertension is a desirable approach to a rare disorder. Currently many patients are screened with angiography, which is both invasive and expensive.

Methods: A MEDLINE search from 1985 through July 1994 using the key words "renovascular hypertension," "noninvasive," "screening" generated 16 references. We reviewed these references, as well as several additional references, in an effort to find a reliable noninvasive screening test for renovascular hypertension.

Results and Conclusions: To date, the most reliable noninvasive screening test for renovascular hypertension is captopril renography. Results of captopril renography allow the physician to diagnose renovascular hypertension with an accuracy of greater than 90 percent. Cost-effectiveness requires appropriate selection of high-risk hypertensive patients for subsequent investigation with captopril renography. Hypertensive patients who have fibromuscular dysplasia, which is most commonly found in young white women, have the best treatment outcomes. (J Am Board Fam Pract 1995; 8:295-9.)

Renovascular hypertension (which occurs in about 1 percent of the hypertensive population) is the most common cause of curable hypertension.[1] Atherosclerosis accounts for nearly two-thirds of renal artery stenosis, fibromuscular dysplasia accounts for approximately one-third, and a small fraction can be attributed to various forms of vasculitis and other rare causes.[2] Although essential hypertension is more common in African-Americans than whites, African-Americans should also be examined for renovascular hypertension, because recent studies indicate that both African-Americans and whites have an equal occurrence of curable renovascular hypertension, and an equally aggressive diagnostic approach is warranted.[3] Overall, healthy young hypertensive women who have renovascular hypertension as a result of fibromuscular dysplasia are those most likely to benefit from early detection, as they have the best treatment outcomes.[4]

Because renovascular hypertension can be cured, routine screening of all hypertensive patients would be ideal. Unfortunately a sensitive and inexpensive screening test does not currently exist. Instead, when renal artery stenosis is surmised to be a cause of hypertension, patients are often screened with angiography. This relatively simple and straightforward procedure is the most sensitive screening test, because it can detect renal artery stenosis sufficient to cause renovascular hypertension. Additionally an angiogram provides surgical information and access for revascularization if it is required. The drawbacks are that angiography lacks specificity, and it is expensive, invasive, and occasionally causes complications. Even after selecting the most likely candidates, only about 30 percent of patients undergoing renal angiography will have sufficiently advanced renal artery stenosis to suggest a renovascular cause for their hypertension; therefore, alternative approaches to screening have been sought.

Methods
A MEDLINE search from 1985 through July 1994 using the key words "renovascular hypertension," "noninvasive," "screening" generated 16 references describing alternative methods of screening for renovascular hypertension; additionally, several other references were consulted.

Results
After a comparison of the sensitivities and specificities of the tests, as well as their availability, captopril renography emerged as the most reliable noninvasive method.[5] Captopril renography

has an accuracy of greater than 90 percent.[6] Screening hypertensive patients for renovascular hypertension with captopril renography also offers a less costly alternative to angiography. At our institution the total cost of captopril renography, including hospital, technical, and professional fees, is $397 compared with $2138 (average cost) for selective angiography of the renal arteries. Patients with a screening captopril renogram that suggests a stenotic renal artery should be referred to angiography for confirmation and for repair, if indicated.

Physiology

A kidney that has a severely stenotic artery releases high levels of renin. Renin cleaves off a peptide from plasma angiotensinogen, and the resulting product is angiotensin I. In the lung angiotensin I is enzymatically converted to angiotensin II. Angiotensin II is a potent systemic vasoconstrictor that also increases renal efferent arterial tone, resulting in increased glomerular capillary hydraulic pressure. This pressure maintains the glomerular filtration rate. Angiotensin II also elevates the systemic blood pressure. The elevated systemic blood pressure improves circulation to the stenotic kidney to the detriment of end organs, notably the heart, brain, and contralateral kidney (unless it is also has a stenotic arterial supply). In addition, angiotensin II stimulates aldosterone, resulting in hyperaldosteronism, which then causes sodium and water retention. Early in the course of renovascular hypertension, this retention is countered by the contralateral kidney, which undergoes a pressure-driven diuresis of the excess sodium and water.[2]

It is advantageous to detect renovascular hypertension at an early stage because the underlying renal stenosis can progress to renal ischemia and renal insufficiency. The contralateral normal kidney might later develop nephrosclerosis in response to continued hypertension. With development of nephrosclerosis, the contralateral kidney cannot compensate for the hyperaldosteronism, and worsening hypertension results.

Investigatory Methods and Limitations

In patients with the late sequelae of renovascular hypertension, the prognosis for cure becomes poor, as does the diagnostic accuracy of all the current screening tests. Also, once nephrosclero-

sis has developed in the normal kidney, it alone can perpetuate hypertension.

Angiography

Although screening renal angiography detects anatomically advanced stenoses (greater than 50 percent), it does not ensure an ironclad diagnosis of renovascular hypertension caused by renal artery stenosis. In fact, some patients without a history of hypertension have had extensive renal artery stenosis at autopsy; therefore, even patients with marked renal artery stenosis might not necessarily have a physiological stenosis, i.e., one that causes renovascular hypertension. As evidence, approximately 20 percent of patients with an anatomically advanced renal artery stenosis are not helped despite successful revascularization.[4] Presumably such patients have a concomitant disorder, i.e., essential hypertension or intrinsic renal disease, that falsely implicates renal artery stenosis as a cause of hypertension. The lack of specificity of the angiogram to implicate renal artery stenosis as a cause of renovascular hypertension leads to complementary renal vein sampling for differential plasma renins from kidneys with renal artery stenosis. Physicians use these studies to attempt to diagnose renovascular hypertension and to establish a relation between renal artery stenosis and the patient's hypertension, as well as to determine which patients would be helped by revascularization or angioplasty. Unfortunately, the renal vein renin studies have not increased the specificity for determining renovascular hypertension, and use of this aspect of evaluation has declined.[7]

Captopril Renography

Angiotensin II maintains the glomerular filtration rate in the kidney with a stenotic artery, and the goal of captopril renography is to eliminate temporarily this compensatory mechanism. Hypertensive patients who have renal artery stenosis will have a diminished glomerular filtration rate, delayed renal flow of the radiotracer as seen in the renogram, and delayed clearance of activity from the affected kidney as depicted in the time-activity curves. Because renal artery stenosis is highly indicative of renovascular hypertension in hypertensive patients, patients with positive test results are referred for angiography.

Certain conditions make diagnosing renovascular hypertension by captopril renography diffi-

cult, such as, (1) stenosis of only one of the many arteries supplying a single kidney, (2) bilateral stenoses (hyperaldosteronism might have developed into the predominant cause of their elevated pressure), (3) intrinsic renal disease including hypertension-induced nephrosclerosis, and (4) renal insufficiency with severe azotemia. These factors confound the ability of captopril renography and other physiological tests to predict renal artery stenosis.

Interestingly, patients with the later sequelae of renovascular hypertension have such a poor prognosis for cure despite successful revascularization that advocates of captopril renography claim it might be the best test for detecting curable renovascular hypertension despite its lower sensitivity when compared with angiography. Such conclusions are premature, and further study is needed to address this issue.

Clinical Screening

Regardless of which screening method is selected, neither is inexpensive; therefore, careful patient selection is important for cost-effectiveness.[8] Unfortunately, there is no established probability of renovascular hypertension in a hypertensive patient with a given set of risk factors. Svetkey, et al.[9] have documented the strong association of an abdominal bruit and refractory hypertension with renal artery stenosis; however, too few patients have been studied using any consistent clinical screening method to establish prospectively a weighting of risk factors. Clinically distinctive features found only with renovascular hypertension and not with essential hypertension do not exist. Consequently, diagnostic testing is adjuvantly used in conjunction with clinical screening. The predictive value and utility of any diagnostic test is better when the prevalence of the disease is high. Given the rarity of renovascular hypertension, the Captopril Renogram Consensus Conference created The Working Party Group for Patient Selection and Preparation, which met and recommended selection of patients with (though not necessarily limited to) the following characteristics[10]:

1. Well-documented, recent-onset hypertension, especially if the diastolic blood pressure is greater than 104 mmHg
2. Known long-standing and well-controlled hypertension that becomes refractory to an existing regimen with no other explanation for resistance to treatment
3. Clinical evidence of generalized vascular disease, i.e., peripheral vascular disease, cerebrovascular disease, aortic occlusive disease, abdominal aortic aneurysms, coronary artery disease, and severe hypertension
4. Hypertension and abdominal bruits, regardless of the time in the cardiac cycle in which the bruit is heard
5. Hypertension and an elevated serum creatinine when no cause can be found to explain the renal dysfunction
6. Moderate to severe hypertension, i.e., diastolic blood pressure greater than 104 mmHg, that develops when the patient is younger than 25 years, especially if the patient is white and not obese
7. Hypertension that is refractory to an adequate three-drug antihypertensive regimen, and no other cause can be found
8. Hypertension with new or worsening renal failure when treated with angiotensin-converting enzyme inhibitors

Regardless of the investigative method chosen, selecting high-risk hypertensive patients for further testing improves the utility of the test, as well as its cost-effectiveness.[9] Deciding which patient is at high risk for renovascular hypertension depends upon the clinical criteria used.

Because captopril renography is not 100 percent sensitive in detecting renovascular hypertension, it should not be undertaken in cases where the clinician will be suspicious of a negative result, e.g., when restenosis is suspected in a patient with an earlier angioplasty and recurrent hypertension. These patients should proceed directly to angiography.

Details of Captopril Renography

After patient selection the patient should discontinue any medications that diminish the sensitivity of captopril renography. Drugs commonly known to interfere — diuretics, which can cause volume loss; β-blockers, which block renin release; and, of course, angiotensin-converting enzyme (ACE) inhibitors — should be withheld for 2 days before captopril renography. If a patient is already receiving an ACE inhibitor and the clinician is reluctant to interrupt therapy, the patient

can skip the base-line study and undergo the challenge part of the study first. If the challenge study results are normal, a base-line study is not necessary; if they are abnormal, however, a base-line study or angiography is advised. If possible, pregnant patients should be excluded from study until after delivery.

The patient should be well hydrated before the study either by drinking 24 oz of water or by receiving a 500-mL bolus (adult dose) of normal saline solution intravenously. Captopril renography uses a renal radiotracer that perfuses the kidneys. Technetium Tc 99m DTPA and Tc 99m mertiatide (Tc 99m MAG$_3$) are the most commonly used agents. Tc 99m DTPA is exclusively filtered through the glomulerus and Tc 99m MAG$_3$ is both filtered and secreted. Although Tc 99m DTPA would appear to have a theoretical advantage because it is most like a glomerular filtration agent, studies have shown Tc 99m MAG$_3$ to have slightly better interpretability because more of it actually enters the kidneys, thus improving visualization and count statistics.[11]

The first part of the study establishes a base-line renogram for both kidneys. After intravenous injection of the radiotracer, dynamic and sequential images of the kidneys are obtained by a gamma camera for 20 minutes. Time-activity curves are generated, which depict passage of the tracer though the kidneys. A stenotic kidney that compensates with renin-produced hypertension might well appear normal in the base-line study.

The second part, or challenge part, of the study entails administering an oral dose of 50 mg of captopril (adult dose) then waiting for 1 hour and reinjecting more radiotracer. This challenge is designed to unmask the kidney with the renal artery stenosis dependant upon angiotensin II to maintain glomerular filtration. In patients already taking an ACE inhibitor, the challenge portion of the test can be done first. A delayed transit time with diminished excretion of the radiotracer is considered a positive test.

Discussion
Considering the rarity of renovascular hypertension, some clinicians might believe that empiric medical management of hypertension would be the better option in view of the cost and difficulty in definitively investigating a patient for this con-

dition. Indeed, for a subset of patients (20 percent) who would not have received benefit from angioplasty or revascularization, medical management would be the best option. For most patients with renovascular hypertension, however, a medical option would entail the deleterious consequences of renal ischemia, diminished renal function, and lifelong aggressive antihypertensive therapy. Angioplasty and arterial stents are making open revascularization procedures less common, and complications with angioplasty are infrequent. Most importantly, patients treated medically have diminished life spans compared with surgically corrected patients.[12]

Nevertheless, clinicians are understandably reluctant to order an expensive, invasive screening procedure of low yield despite the success of renovascular hypertension treatment; alternately, waiting until more convincing clues, such as renal insufficiency, have developed would diminish the chance for detection and cure. A noninvasive modality is therefore worthy of consideration for early screening for renovascular hypertension. Captopril renography used in conjunction with appropriate clinical screening provides such a noninvasive cost-effective approach to investigating high-risk hypertensive patients for renovascular hypertension. The mean sensitivity and specificity derived from several studies are 92 percent and 94 percent, respectively.[11]

Other noninvasive methods to screen for renovascular hypertension include Doppler sonography, which is also highly sensitive and specific in detecting renal artery stenosis in the hands of experienced operators. Doppler sonography for detection of renal artery stenosis is not widely practiced, however, even in large medical centers. Overall technical failure rate is high, because bowel gas, patient movement, and difficulty in visualizing the entire renal artery greatly reduce its accuracy. Magnetic resonance angiography is being attempted to diagnose renal artery stenosis but is still in the research stage.

Captopril-stimulated plasma renin analysis is also another noninvasive screening test for renovascular hypertension in which oral captopril is used to stimulate plasma renin release by stenotic kidneys. Base-line plasma renin levels are compared with plasma renin levels following captopril administration. Although inexpensive, this test requires patients be free of antihypertensive medications for

3 weeks before testing and has a low sensitivity and specificity, 76 percent and 82 percent, respectively.[5]

In selecting captopril renography instead of angiography to screen patients at high risk for renovascular hypertension, the clinicians at our institution accept a screening modality that is 92 percent sensitive for renovascular hypertension, that is noninvasive, and that costs $397 (technical and professional fees included). Alternately, angiography ensures 100 percent sensitivity for detection of a renal artery stenosis that might be the cause of the patient's hypertension, but it is invasive, and the contrast medium can be nephrotoxic. Selective angiography of the renal arteries, including professional, technical, and miscellaneous fees, costs approximately $2138 at our facility. Based on costs at our institution and assuming that 30 percent of clinically screened patients will have a positive captopril renogram and will require angiography to confirm the diagnosis, a cost analysis can be calculated for screening 100 patients with captopril renography compared with angiography only:

1. Cost of screening with angiography only — $213,800.
2. Cost of screening with captopril renography followed by angiography in 30 percent of cases — $39,700 + $65,490 = $105,190. (These assumptions do not take into account the approximately 8 percent of patients who have renovascular hypertension that will not be detected with captopril renography.)
3. Net cost savings $213,800 less $105,190 = $108,861 per 100 patients screened or $1088 per patient screened.

In summary, for patients or clinicians who desire a noninvasive and more cost-effective screening method than angiography for detection of renovascular hypertension, captopril renography is an excellent alternative.

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