MANAGEMENT OF RENOVASCULAR DISEASE

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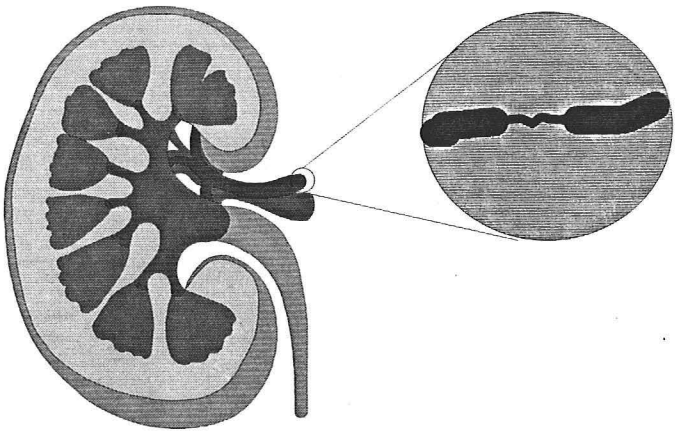

MEDICAL GRAND ROUNDS
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HISTORY OF RENOVASCULAR HYPERTENSION

Kidneys contain a pressor substance

In 1898, Tigerstedt and Bergman prepared a saline extract of rabbit kidneys, injected it back into healthy rabbits and produced an instant rise in blood pressure (Tigerstedt 1898). They postulated that kidneys contain a water-soluble pressor substance which they termed "renin". Their observation were disputed and the existence of renin was questioned for many years because other investigators could not reproduced their results due to methodologic difficulties in preserving biologically active renin.

The seminal work of Dr. Harry Goldblatt

The physiologic significance of this pressor substance was not appreciated until the 1930's when Dr. Harry Goldblatt and coworkers performed a series of experiments that constituted the first still to this day the only experimental model of renal vascular hypertension (Goldblatt 1934). Dr. Goldblatt's interest was in primary hypertension and in the late 1920's, he was searching for an animal model that he could use to study pathogenesis of human hypertension. Being a surgeon and a pathologist, he noted on autopsies that no matter the mode of death, whether it was cerebral, cardiac or renal, diffuse vascular renal disease was highly prevalent in patients with hypertension. The prevailing dogma at the time was that diffuse vascular renal disease was a result of hypertension. Since there was no data, Dr. Goldblatt contested that there was no *a priori* reason why hypertension has to preceed the vascular disease and raised the counter argument that renal vascular disease may cause hypertension (Goldblatt 1990). In 1928, Dr. Goldblatt and coworkers went ahead and tested the validity of this contention. Since they had no means of producing diffuse vascular disease, they simply simulated the hemodynamic effects of reduced vessel calibre by partially clamping the main renal artery.

A series of experiments were performed. In their first paper, these investigators applied clamps on renal arteries on dogs to reduce renal blood flow and observed a sustain rise in systemic blood pressure (Goldblatt 1934). A dose effect can be demonstrated, when renal blood flood was progressively reduced as measured by renal venous outflow, by tightening the clamp. These invesigators showed that this effect was present even when the ischemic kidney was denervated. It was present when the adrenal glands are removed, But it was absent when non-renal splanchnic arteries were constricted. Based on these observations, they postulated that the ischemic kidneys may increase the output of some internal secretion which, by peripheral or central action, causes general vasoconstriction and raise the blood pressure. In the next few years, a number of experiments were performed by Goldblatt and others that expanded on the original observation. One key experiment was performed by Harrison and coworkers in 1936 (Harrison 1934). Saline extracts were taken from either control or ischemic kidneys from dogs and injected into healthy

dogs. The extract from ischemic renal tissure caused a greater rise in blood pressure than extract from the opposite normal kidney proofing that a "hypertensive substance" is generated distal to an ischemic kidney. This "hypertensive substance" of course was renin.

The first clinical report of renal vascular hypertension appeared in 1938 (Leadbetter 1938). Two urologists at Johns Hopkins described a young boy who presented with blood pressure of 220/110 with normal renal function by blood chemistry. On IVP, left kidney was normal but there was very poor or absent visualization of the right kidney. On retrograde pyelograms, they found an intact right collecting system that was situated in the pelvis. In the operating room, they found an ectopic right kidney over the iliac vessels. Since this kidney had no function on IVP, they decided to remove it. Immediately after the nephrectomy, the boy's blood pressure dramatically returned to normal. It became clear that the ectopic kidney must have been the culprit. The pathology surprising showed fairly normal kidney architecture other than some cortical thinning. The striking finding was in the main renal artery which was partially occluded by a smooth muscular plug. Leadbetter and colleagues recognized the resemblance of their patient to Goldblatt's experiments and presented their case as a clinical example of Goldblatt's renovascular hypertension. In their discussion, they stated: "There is no doubt that disease of renal arteries, one or both, which results in partial occlusion can be the cause of certain cases of hypertension..... in these cases, nephrectomy of the affected kidney provides a cure for the hypertension."

Clinical practice (or malpractice)

This very convincing case report was amidst dozens of other ones some of which were not as convincing as the one by Leadbetter but nonetheless begot the notion that unilateral renal disease with hypertension is curable by nephrectomy. By 1945, 242 cases had emerged in the literature of unilateral renal diseases that were nephrectomized for the purpose of attempting to cure the associated hypertension. There were of course countless number of others that were not reported. By the mid 1940's, the surgical dogma was entrenched that patients with a unilaterally abnormal IVP and hypertension should be adviced to have a nephrectomy. In 1947, Homer Smith reviewed of the cumulated literature to date and stated his criticism to the widespread practice of nephrectomy in a very articulate review (Smith 1947). Smith pointed out that the incidence of hypertension is not significantly increased in patients with urologic diseases and that the incidnece of urologic diseases were not increased in patients with hypertension. In the reported cases, only 19% of patients had partial of complete relief of their hypertension. A figure way too low to warrant nephrectomy in all patients. The major reason for this initial failure was that most unilateral urologic disease were either reflux, calculi or obstruction. Naturally, removal of the affected kidney would not cure the hypertension. This inaccuracy in diagnosis is of course no longer an issue since the introduction of angiography. However, Homer Smith made a point which is still illustrates one of the most difficult problem in managing

renovascular disease today. He specified that the cause of essential hypertension is unknown and there is no data that points convincing to the primacy of renal ischemia. Even Harry Goldblatt wrote ten years after the publication of his first model that all his experiments elucidated humoral mechanisms found to be directly responsible for elevation of blood pressure really only apply to those type of human hypertension associated with renal vascular disease.

Even in the 1940's, both Homer Smith and Harry Goldblatt realized that renal ischemia only accounts for a small fraction of patients with hypertension and one must not recommend corrective procedures based solely on the hope that it may help the patient.

CASE PRESENTATIONS

Four patients will be presented and several questions will be posed.

1. Young white female with hypertension

This is a 30 year old white female who has been in perfect health with normal blood pressure documented a year ago. She developed headaches and her physician found her pressure to be 200/100. Her pressure was eventually controlled with benazepril 20 mg qd and amlodipine 10 mg bid. Her past medical and family history was negative. She had no other symptoms suggestive of secondary hypertensive states. On examination, she had a blood pressure of 140/85. There were no other findings other than some mild AV-nicking in the optic fundi. Her electrolytes were normal and her serum creatinine was 0.8 mg/dl. The rest of the laboratory data did not reveal any evidence of either secondary hypertension or significant end organ disease except for 300 mg/24 hrs of proteinuria. Given the rapidity and severity of her hypertension, one will no doubt be alerted to the the possibility of renovascular hypertension. In this age group, one is dealing primarily with fibromuscular dysplasia (FMD).

1. Is there any value in doing a renal captopril scan? Should one go through the trouble of stopping her benazepril? Is a renal scan neccessary or,

2. Should one just proceed to arteriography? Is that too invasive? Can a negative renal scan save the patient from arteriography? And if the scan is positive, one will have to proceed to angiography if intervention is contemplated. With this line of reasoning, one may ask why do renal scans at all.

3. What should one do if a renal arterial lesion is found? Should one elect to have angioplasty or surgery. Surgery should be well tolerated in a patient such as this one. Is surgery better? Is there a role for medical therapy? Can one just follow and treat this patient medically since her pressure is well controlled and her renal function is normal?

2. Young black male with hypertension

Next consider a 35 year old black male first presented 3 years ago with a blood pressure of 200/110. At that time, except for grade 2 retinopathy, his physical examination and laboratory evaluation was all negative. He has been treated for the last three years and his blood pressure control has been difficult. His blood pressure is now 150/90 on on nifedipine, lisinopril, furosemide, and labetalol. His creatinine clearance is 95 cc/ml but he has 800 mg of proteinuria/24 hours and mild left ventricular hypertrophy on echocardiogram and EKG. His doctor decided to rule out

renal artery stenosis and ordered a captopril scan. The patient forgot to hold his medicines prior to the scan, therefore one scan was performed with the patient on lisinopril and it was completely normal.

1. What is the probability of this patient having renovascular hypertension?

2. Should one just do an angiogram ?

3. What is the utility of a captopril scan in this patient? Is a normal scan adequate to rule out the diagnosis?

4. If a renal artery lesion is found, does he have renal artery stenosis or renovascular hypertension? Do renal vein renins help?

3. An elderly male with hypertension, congestive heart failure and deteriorating renal function.

The third patient is a 65 year old male who was admitted to the medical ward for left ventricular failure. This patient has been a smoker all his life and suffered from hypertension for 17 years. His pressure was well controlled initially but in the last 3 years he required escalation of antihypertensive therapy on multiple occasions. This current admission is the second episode of pulmonary edema in the last 6 months. He also has a history of stable angina for two years. His serum creatinine S_{Cr} which was 1.3 mg/dl two years ago, has risen to 2.0 mg/dl one year ago, and now has a baseline of 2.5 mg/dl. His urinary sediment was always benign and his 24 hr urine protein has been less than 500 mg/24 hrs. Sonogram of his kidneys a year ago showed a left kidney of 10.7 cm and a right kidney of 9.2 cm. His admission medications were captopril, diltiazem, furosemide, KCl, isosorbide, and digoxin. On examination on admission, his blood pressure was 200/110, The patient was in pulmonary edema. He had grade II retinopathy. Pulses were reduced diffusely and bruits were heard over the carotids, epigastrium, and femorals. EKG showed LVH with strain and CXR showed an enlarged heart and pulmonary edema. His admission S_{Cr} was 3.2 mg/dl which was higher than his baseline. The patient was admitted to hospitala and was ruled out for a myocardial infraction. His pulmonary edema resolved after a diuresis of 4 kgs. However, his S_{Cr} creatinine rose to 6 mg/dl. His diuretics and captopril were held and over the next 4 days his S_{Cr} decreased to 4.5 mg/dl. Finally, he came into a steady state with a S_{Cr} of 2.9 mg/dl and was free of CHF symptoms.

1. Does this patient have renal artery stenosis? If he does. Does he have renovascular hypertension superimposed on his primary hypertension?

2. Is the renal artery stenosis contributing to his acute renal failure and his chronic renal insufficiency?

3. How should one make the diagnosis of renovascular hypertension in this case? Can one trust a renal scan in this patient? Should one proceed to arteriography knowing that both the intraortic instrumentation an the contrast will be detrimental to his diminished and dwindling renal function.

4. If renal artery stenosis is found, what should one do? Would angioplasty help? Should one commit this patient to renal surgical revascularization knowing that he may have coronary artery disease and cerebrovascular disease? If surgery is attempted, what are the chances of improving blood pressure control and renal function?

5. If one elect not to operate, what are the chances of this man progressing to end stage renal failure? What are his chances of surviving the next five years.

4. An elderly man with a 70% stenosis of the right renal artery

The last patient is a 60 year old man who has a history of coronary artery disease that was bypassed 10 years ago. He has done well except for some hypertension which was controlled on a beta blocker. He renal function is completely normal. He developed some recurrence of chest pain and had some equivocal noninvasive studies. A repeat cardiac catherization was performed which showed patent coronary bypass grafts. Incidentally, he was found to have an abdominal aortic aneurysm measuring 6 cm in transverse diameter and a left renal artery stenosis of 25% and a right renal artery stenosis of 70%. The vascular surgeons recommended elective repair of his aortic aneurysm and possibly right renal artery bypass.

1. Should one fix a renal artery stenosis in a patient with perfectly controlled blood pressure and normal renal function?

2. Are there any tests that one can do to predict whether this 70% lesion will cause renal failure in this 60 year old?

INTRODUCTION

Renovascular stenosis is not equal to renovascular hypertension

Renovascular stenosis is a descriptive anatomic diagnosis of a reduction in calibre of renal vessels. Mere demonstration this structual defect is not sufficient to make the diagnosis of renal vascular hypertension. Two well established clinical observations secures this notion. First, atheromatous renal artery lesions, from mild to moderate to severe, are commonly found in normotensive patients. Holley and coworkers examined 295 autopsies and demonstrated renal artery stenosis in 77% of previously hypertensive patients but similar lesions were found in 57% of previously normotensive patients (Holley 1964). In an analysis of 500 aortograms performed for peripheral vascular disease, renal artery stenosis was found in 63% of hypertensive patients but also in 32% of normotensives (Eyler 1962). Second, many hypertensive patients undergo successful correction of the arterial obstruction but avail no relief of their hypertension whatsoever from the revascularization. We will discuss this annoying result in a little more detail later.

A strict definition of renovascular hypertension requires absolute fulfillment of all three of the following criteria.

1. Renovascular disease
2. Hypertension
3. Hypertension relieved with anatomic correction

The third criteria can only be met with a therapeutic intervention. Still to this day, we do not have a reliable way of distinguishing a patient with primary hypertension and renal artery stenosis from one with renal vascular hypertension without trying to correct the lesion. This definition although is correct in principle, may be too stringent to fulfill in practice. Two more facts further complicate the situation. First, a frequently encountered scenario is a patient with both renovascular hypertension as well as primary hypertension. Second, a patient with longstanding renovascular hypertension may develope renal parenchymal disease that itself can lead to hypertension. In both of these cases, some or a large degree of hypertension will persist even after correction of the vascular lesion.

A second presentation of renovascular disease: Ischemic nephropathy

In addition to hypertension, renovascular disease can present in another fashion. Ischemic nephropathy is reduction in glomerular filtration in patients with hemodynamically significant renal artery obstruction. It is sometimes difficult to distinguish this patient from the one with nephrosclerosis secondary to hypertension. This syndrome as a seperate entity is only recognize recently (Novick 1983, Jacobson

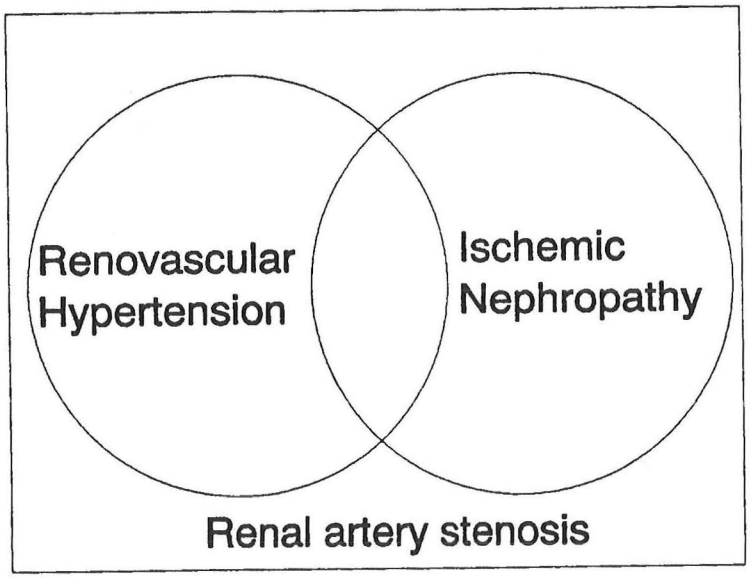
1988, Rimmer 1993, Breyer 1993). The ultimate patient that fits this syndrome will be someone with diffuse atherosclerosis who is not hypertensive, has minimal or no proteinuria and has progressive renal insufficiency from no identifiable etiology. This patient gets studiedwth renal angiograms that document bilateral renal artery stenosis, undergoes bilateral reconstruction and his renal insufficinecy improves dramatically. However, the most common presentation of this syndrome is chronic progressive azotemia in a hypertensive vasculopath. Another presentation is simply end stage renal failure with bilateral atrophic kidneys downstream from renal arteries that have progressed to complete occlusion. An acute reversible form of this syndrome is acute renal failure precipitated by acute drop in blood pressure, effective arterial volume, or both. We will discuss this syndrome a little more later.

A third "presentation" of renal vascular disease

Patients in the third syndrome of course do not present because they are asymptomatic. However, with the use of angiography in investigating periperal vascular, aortic, or coronary artery disease, patients with renovascular disease can now present with an abnormal angiogram but is completely normotensive with normal renal function. It is completely unknown whether such a compensated patient will develope future clinical complications.

The spectrum of renovascular disease can thus be classified into three overlapping syndromes.

SYNDROMES OF RENOVASCULAR DISEASE

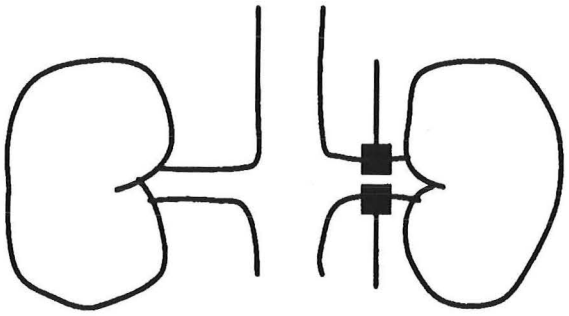


WHY FIX A STENOSED RENAL ARTERY

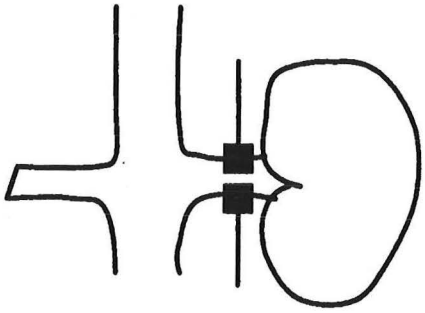
The only reason for looking for renovascular disease is a realistic likelihood of response to revascularization. At the present time, there are only two indications for revascularization. One fixes renal arteries to treat hypertension and preserve and/or salvage ischemic renal tissue. To understand whether revascularization would help hypertension or renal failure, one should try to understand the pathophysiology.

Pathophysiology of renovascular hypertension in animal models

There is a large body of literature on this subject based on variations of the original experiments by Goldblatt. A few findings and concepts will be highlighted to help understand human renovascular hypertension. There are basically two designs in animal models. The two kidney one clip model which is equivalent ot unilateral renal artery stenosis. And the two kidney two clip which for practical purposes is the same as the one kidney one clip model. This model simulates human bilateral renal artery stenosis or unilateral stenosis in a functionally solitary kidney.



2 KIDNEYS 1 CLIP



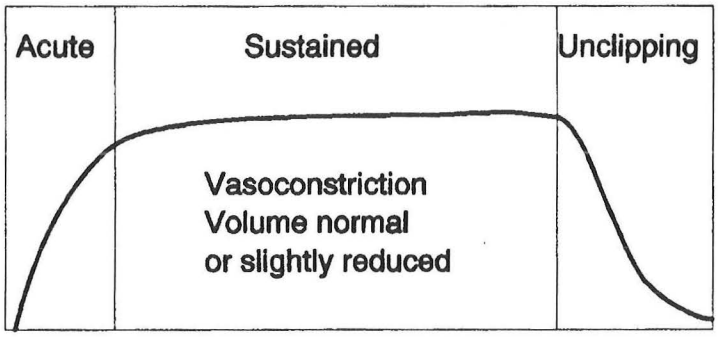
1 KIDNEY 1 CLIP

Pathogenesis of hypertension is different depending the phase of the model and the species. The acute phase of hypertension is basically the same in both models. After the clip is put on, blood pressure rises instantaneously. This is the prototype of acute hyperrenin hypertension mediated by vasoconstriction. Plasma renin and angiotensin II levels are sky high (Swales 1971, Mohring 1975). The hypertension can be induced even if the animals are adrenalectomized and kidneys are denervated (Goldblatt 1934). Administration of converting enzyme inhibitors and angiotensin receptor blockers prevents or reverses the hypertension (Brunner 1971, Anderson 1990). This phase is short-lived and resembles human renovascular hypertension only in settings such as acute renal artery thrombosis, embolic obstruction or vasculitis.

After a few days of clipping, blood pressure continues to increase but renin angiotensin II, and aldosterone levels begin to drift down. The pathophysiology of the hypertension at this stage becomes rather complex and differs depending on the model, the species and the volume status of the animal.

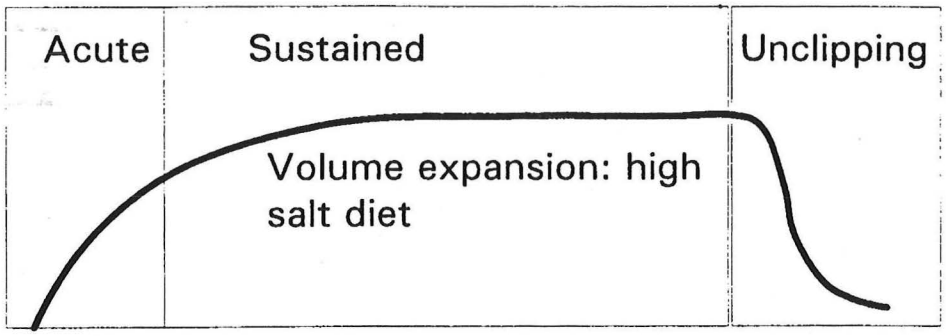
The 2K 1C model is probably more analogous to human unilateral renovascular hypertension than the 1K 1C is to bilateral renal renovascular hypertension. After the clip is applied, the ishemic kidney elaborates large amounts of renin and renin production in the contralateral kidney becomes maximally suppressed. There is a direct correlation between the blood pressure and peripheral renin but the correlation is partcularly strong between blood pressure and renal vein renin from the ishemic kidney (Leenan 1973). This experimetal finding is the basis for the clinical lateralizing renin test. Systemic pressure is maintained largely by vasoconstriction. The hypertension in these animals remains angiotensin-dependent and they manifest hypotensive responses to ACEI throughout (Brunner 1971, Gavras 1973). Although chronically, plasma renin, angiotensin and aldosterone levels fall towards normal. No point in time is there a positive Na balance nor is plasma volume significantly expanded (Tobian 1969). The presumed reason is that the normal contralateral kidney can excrete Na normally. Upon removal of the clip, blood pressure falls to normal levels within 24 hours accompanied by a fall in peripheral vascular resistance and interestingly a positive Na balance (Thurston 1980, Russell 1981). One possible explanation for the positive Na balance is that the contralateral kidney that was that was reset to effect pressure natriuresis during the hypertesnive phase is now experiencing a relatively "low" blood pressure and responds with antinatriuresis. The rapidity of the response suggests that structural remodelling is not required for reinstatement of normotension. The hypotensive response to unclipping was evident even when the animals were pretreated with ACE inhibitors (Russell 1982). The authors concluded that humoral factors other than the renin-angiotensin system may be involved. An alternative interpretation of this findings is that the intrarenal autocrine and paracrine angiotensin systems are not inhibited by systemic doses of ACE inhibitors.

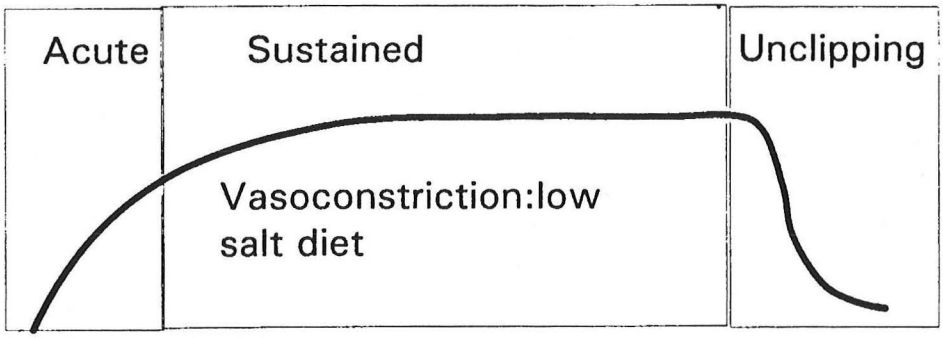
2 KIDNEYS 1 CLIP MODEL



In the chronic phase of the 1 K 1 C model, there is expansion of plasma volume occuring as a result of sodium retention with normal or low renin levels if the animal ingests a normal salt diet. This is thus an example of high volume low renin hypertension. If a coverting enzyme inhibitor or AII receptor antagonist is given, the blood falls very modestly, if at all (Brunner 1971, Miller 1975). Although there is no acute response, when ACEI are continued over a long period of time, a natriuresis ensues that returns plasma volume and blood pressure towards normal (Bengis 1979). When the animal is placed on a salt-restricted diet, plasma volume normalizes but blood pressure surprisingly still remains elevated (Rocchini 1979). Only now, renin and angiotensin levels are high, and blood pressure normalizes with ACEI adminstration (Gavras 1973, 1975). Therefore, the pathophysiology of hypertension in the chronic phase of the 1 k 1 C model is highly dependent on the salt intake or volume of the animal. Upon unclipping, animals with the 1 K 1 C model also restores their blood pressure to normal (Liard 1980). Consistent with the volume expansion hypothesis stated above, the fall in blood pressure can be correlated with degree of natriuresis. The vasoconstrictive component of the hypertension is demomnstrated by the fact that NaCl replacement during natriuresis does not totally prevent the fall in blood pressure (Neubig 1975).

1 KIDNEY 1 CLIP MODEL





Relevance of animal models to human renovascular hypertension

The relevance of these model to human hypertension at present can only be inferred. One thing for certain is that the mechanisms uncovered in animal models are too simplistic to explain the spectrum or human disease. Unilateral fibromuscular disease in humans is probably well simulated by the 2K 1C model in rats. For human atherosclerotic renal artery stenosis, the situation is much more complex. One must remember especially for atherosclerotic diseases, there are no pure models in humans. One rarely sees true unilateral atherosclerosis. On the other hand, bilateral renal artery stenosis is rarely symmetrical. The only real human equivalent of the 1K 1C model is unilateral stenosis in a solitary kidney. Second, the pathogenesis of hypertension is likely far more complicated than what is proposed. Since all of these studies were done prior to the discovery and characterization of intrarenal renin angiotensin systems, local autocrine and paracrine effects of AII which is undoubtedly going to be important, has not been studied in these models. Third, there is a large body of literature implicating participation of neural sympathetic. kinins, nitric oxide, and other hormonal systems in the pathogenesis of hypertension in these models. These findings suggest that the situation is a lot more complex than what has been conjured. However, it is very difficult to interpret these findings in a unified way because a lot of the changes can be results of or compensations for hypertension and ischemia rather than causative.

The following observations in humans resemble the animal models. Any single one of these observations is weak and by no means proves the validity of the model. However, in combination they do lend some support the notion.

1. In patients with unilateral renal artery stenosis, plasma renin activity tend to be high or normal, but are uncommonly low (Brown 1965).

2. When acute unilateral ischemia was induced in humans (Fiorenti 1981), renal vein renin lateralized to the ischemic side with contralateral suppression. Chronic ischemia tends to lateralize towards the ischemic kidney or not lateralize. The reverse seldom occurs.

3. When plasma renin activity is normal, volume tended to be higher than primary hypertensives (Bianchi 1970).

4. There is positive correlation between exchangable Na and blood pressure in essential hypertension but in renovascular hypertension, there is a negative correlation (Davies 1979). This resembles the 2K 1C model where the normal kidney excrete Na avidly.

5. In a series of 51 cases of bilateral stenosis or unilateral stenosis of a solitary kidney, one quarter of these patients developed pulmonary edema at some point.

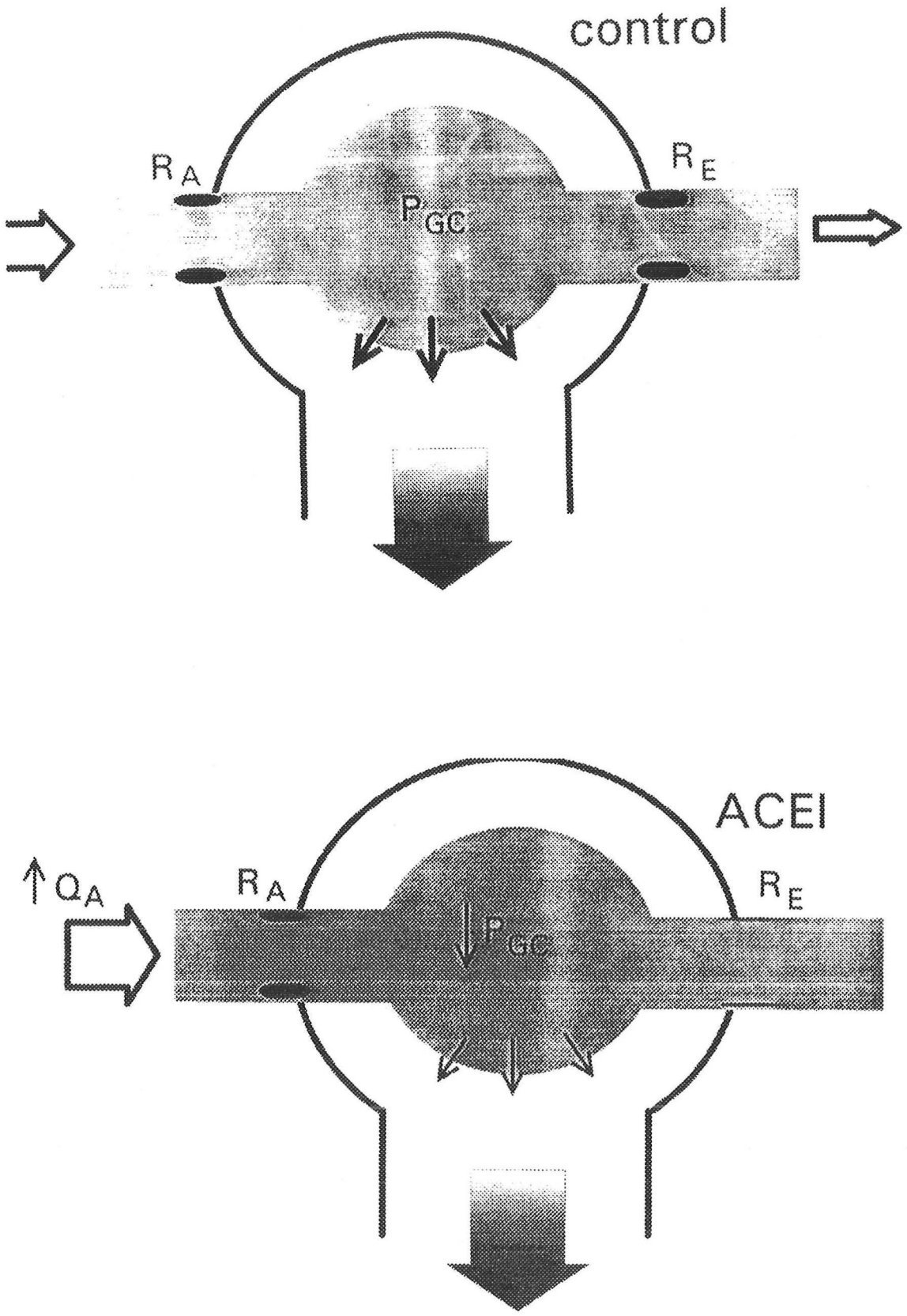
Although the high incidence of coronary artery disease can partly explain this complication, the fact that renal revascularization dramaticall decreased the incidence of pulmonary edema suggest derangement in volume regulation in bilateral renal artery stenosis (Pickering 1987).

6. There are reports of natriuresis following successful revascularization in bilateral disease (Sutters 1987).

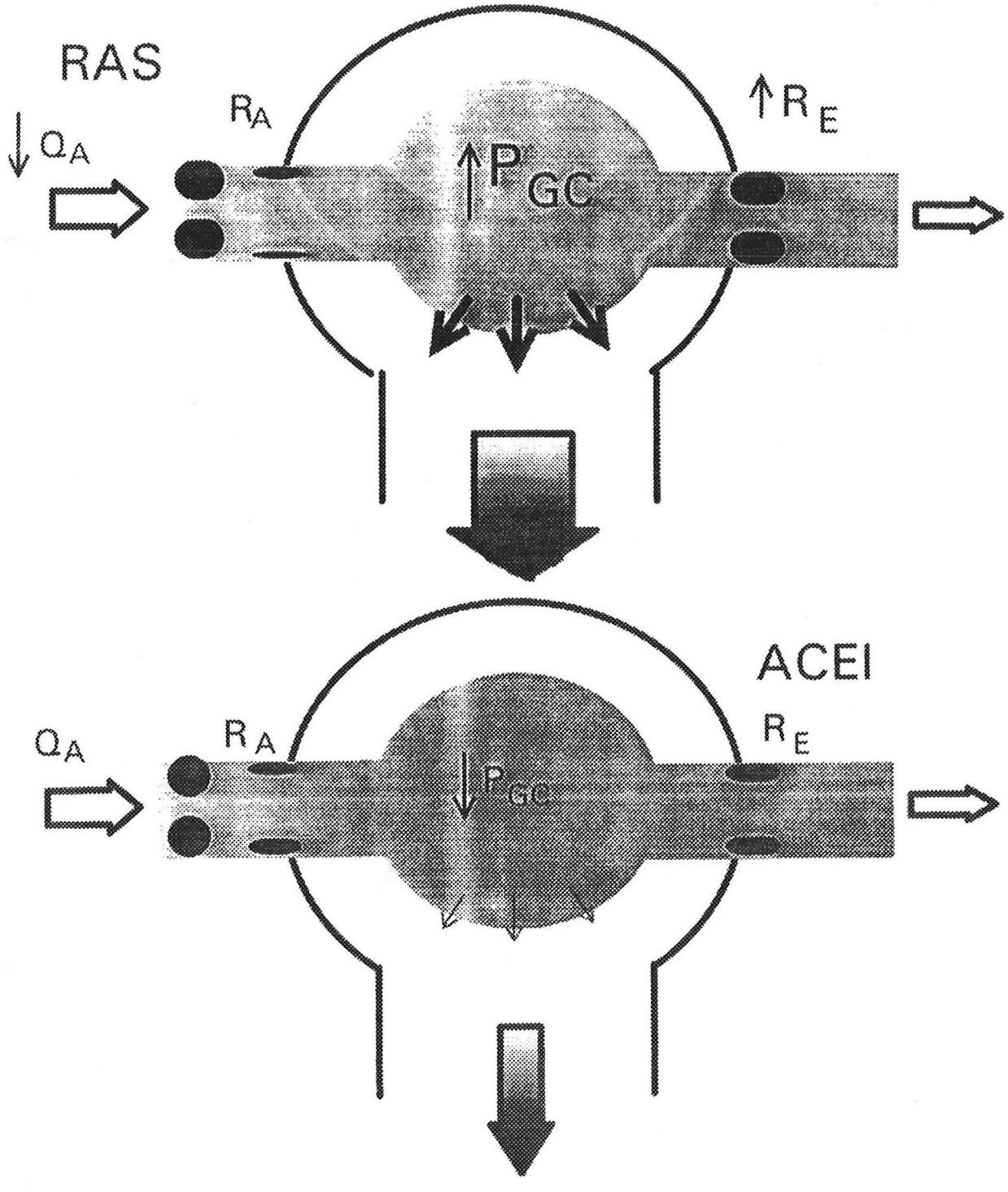
In summary, there is little doubt that renal artery stenosis can cause hypertension in humans. The pathophysiology of human renovascular hypertension resembles the animal models in certain aspects but differs sufficiently to caution generalization of the animal data. Unilateral fibromuscular dysplasia and the rodent two kidney one clip model probably shares the greatest similarities. Atherosclerotic renovascular hypertension is less adequately explained by the pathophyiology of the animal models. Human renovascular hypertension is most likely dependent on the renin-angiotensin system involving both excess circulating volume and vasoconstriction.

Pathophysiology of renal failure

The pathophysiolgy of acute reversible deteriorations in renal function in renovascular disease is much better understood than the chronic irreversible form of the syndrome. Acute renal failure is seen in situations of acute fall in systemic blood pressure due to volume contraction or adminstration of antihypertensives. In the glomerulus, angiotensin II has a greater vasoconstrictive effect on the efferent (or post-glomerular) arteriole than the afferent (pre-glomerular) arteriole. One can imagine glomerular filtration rate (GFR) to be determined by renal plasma flow (Q_A), the glomerular capillary ultrafiltation pressure (P_{GC}), and the ultrafiltration coefficient of the filtration barrier (K_f). When an ACE inhibitor is administered to a normal individual, preferential efferent arteriolar dilation will impart three effects. A fall in P_{GC} will tend to decrease GFR, and an increase in Q_A and K_f will tend to increase GFR. The net result is that GFR remains constant or it may actually increase a little. Alternatively, when systemic BP falls, Q_A is overall maintained unless the fall of BP is dramatic, but P_{GC} will tend to fall threatening to decrease GFR. Increases in the resistance of the efferetn arteriole will tend to maintain $P_{GC.}$

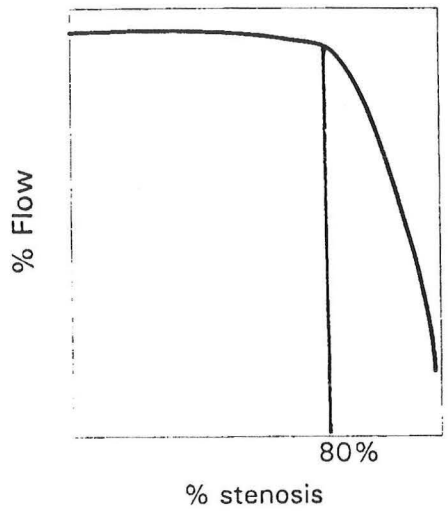

control
R_A
R_E
P_{GC}
ACEI
$\uparrow Q_A$
R_A
R_E
$\downarrow P_{GC}$
GFR maintained

In the presence of a fixed stenosis. The baseline glomerular hemodynamics are positioned differently due to a heightened AII state. Resistance at the afferent arteriole (R_A) tend to be slightly lower and that of the efferent arteriole (R_E) is higher. Although Q_A is reduced in this condition, GFR is maintained mainly by a very high P_{GC}. When ACE inhibitors are given, P_{GC} falls. But unlike the normal individual who can increase Q_A to compensate, Q_A is limited by a physical obstruction and hence cannot increase. A fall in effective circulating volume or system BP even in the absence of ACE inhibition can no longer be buffered by increase in R_E because R_E is likely already close to its maximal capacity. The net result is that GFR falls.



This effect was studied under control conditions by Textor and coworkers in humans (Textor 1985). When systemic pressure were lowered in a controlled graded fashion. In 8 patients with unilateral renal artery stenosis, GFR and RPF was maintained despite systemic hypertension. This has been ascribed to compensation by the normal contralateral kidney. In contrast, in 8 patients with bilateral renal artery stenosis, both GFR and RPF were reversibly decreased. When these same patients were restudied after successful vascularization, falls in GFR and RPF were no longer evident with systemic hypotension.

The mechanisms of chronic ischemic renal failure is not well studied at all. Compared to the amount of animal experimentation done on renovascular hypertension, chronic ischemic renal failure has hardly been studied in animals. The only studies available seem to indicate no more than the fact that the condition exists in rats but really have provided limited insight into the mechanisms of the chornic injury (Textor 1988, Grone 1986, Michel 1986). Paradigms associated with acute renal ischemia causing tubule necrosis have little or no validity in chronic ischemia. Pathology in human kidneys attributed to "chronic ischemia" includes collapse of glomeruli with duplication of basement membrane. As the lesion advances, diffuse sclerosis of glomeruli are observed. Juxtaglomerular hypercellularity is prominent. Loss of tubular integrety, chronic interstial infiltrate and fibrosis (Rimmer 1993, Wiggins 1989). Most of these changes are non-specific and all of them can be secondary to hypertension, diabetes or aging itself. Note that although one is referring to large renal arterial disease here, the lesion of diffuse small vessel atherosclerosis can cause a syndrome identical to that of renal artery stenosis. We are not addressing small vessell disease in our discussion of management because they are not amenable to surgery.



The concept of critical arterial stenosis was first introduced by May and coworkers (May 1963). Graded stenoses in do not lead to significant falls in flow or pressure drop until the stenosis reaches a critical value. After that both flow and pressure falls precipitously (May 1963). Studies in other vascular beds indicate that lumen cross-sectional narrowing must exceed 80% to 85% before measurable decrements in either pressure or flow developes (May 1963). Since obstruction to flow is a function of the percentage luminal narrowing as well as absolute luminal diameter, length of the stenosis, and blood flow rate. The critical inflection point will vary from artery to artery and for a given artery, changes in cardiac output and systemic blood pressure will shift the point of critical stenosis. Using these parameters, May and coworkers mathematically modelled different arteries in the body and correlated the predicted results with measured animal values (May 1963, Haimovici 1962).

Both the modelling and canine measurements indicate critical renal artery stenosis typically occurs around 70-80% luminal area. Human data from patients studied by May and coworkers showed the following.

Subject	Renal artery assessment		pressure (mm Hg)		
	Arteriogram	Intraoperative	proximal	distal	fall
1	-	mild	130	130	0
2	-	mild	85	85	0
3	-	mild	130	125	5
4	82%	moderate	220	128	92
5	84%	moderate	150	135	15
6	97%	severe	150	80	70
7	97%	severe	170	20	150

In humans, fall in perfusion pressure distal to the stenosis was not seen in lesions smaller than 80%. It is important to recognize that the correlation between the magnitude of stenosis and pressure gradient is quite variable.

In the kidney, two unique features render it difficult to extrapolate these data to the renal circulation. First, renal blood flow is extremely well autoregulated over a wide range of aortic pressures. Lowering of renal blood flow is not detected until arterial systolic perfusion pressures are reduced to 70-80 mm Hg in acute studies (Grangsjo 1972, Hall 1977, Ofstad 1985). This requires a significant gradient across the stenosis to decrease renal perfusion. However, autoregulation of renal blood flow is effected by a combination of myogenic reflexes and tubuloglomerular feedback mechanisms. It is plausible that chronic demands on activated autoregulation by low perfusion pressure may indeed elicit compensatory mechanisms such as intraglomerula hypertension that are deleterious to glomerular function.

Second, the kidney recieves 20% of cardiac output which translates to 1 L/min or 4 ml/min/gm tissue. In contrast to other organs, the kidney is very luxuriously perfused. A significant portion of renal blood flow is utilized for excretory function with less than 10% oxygen extraction (Ofstad 1985). A glance at the comparison of Oxygen delivery to and comsumption by various organs illustrate this point.

Organ	O_2 delivery ml/min/100 g	O_2 consumption ml/ml/100 g	Consumption % delivery
Kidney	84	6.8	8
Brain	11	3.7	34
Skeletal muscle	0.5	0.2	34
Cardiac muscle	17	11	65

As a result, the renal vein has the highest oxygen tension and content of all venous blood. From these standpoints, it is very difficult to realize how the kidney would be prone to ischemia. Paradoxically, the unique architecture of the kidney however does creat in the renal medulla one of the lowest oxygen tensions in non-contractile tissues. At the medullary tip, oxygen tensions can reach 10 mmHg.

This relative tissue hypoxia has been employed to explain the pathogenesis of acute tubular necrosis from circulatory collapse. However, in chronic renal artery stenosis, it is actually not known whether there is any degree of tissue hypoxia. Weicek and coworkers examined venous pO_2 and erythropoeitin levels in 19 patients with unilateral renal artery stenosis (Weicel 1992).

	Arterial	Caval	Normal kidney	Kidney with RAS
Renin (ng/ml/h)	5	3	3	7
pO_2 (mm Hg)	99	42	51	53
Epo (mU/ml)	17	16	16	16

Despite lateralization of renal vein renins which is a marker for decreased solute delivery, there was no oxygen desaturation or detectable erythropoietin elevation in the renal vein. If hypoxia is present, it is either very mild or occurs only regionally.

The bulk of the data supporting the existence of this syndrome is derived from clinical studies. The first indirect evidence is from demographic data from end stage renal disease programs. Mailloux and coworkers reported 83 out of 683, or 12% of their dialysis patients over twenty years as having end stage renal failure due to chronic ischemia based on the following criteria: 1. generalized atherosclerosis, 2. minimal proteinuria, 3. benign urinary sediment, 3. renal artery stenosis defined by either angiogram or significant isotope scan (Mailloux 1994). Scoble and coworkers (Scoble 1989) estimated in their dialysis and transplant program a 6% incidence of renal vascular disease as a major cause of renal failure (Scoble 1989).

Wollenweber was the first to point out in a retrospective series in the 1960's

that chronic renal insufficiency complicates renal artery stenosis (Wollenweber 1968). He studied 109 patients and showed that 15% of them were azotemic at presentation (BUN> 50 and PCr >2) and over a mean period of 42 months, 12% of the originally non-azotemic patients developed azotemia. Unfortunately, the retrospective data presented did not allowed one to exclude the role of hypertension per se in causing the deterioration in renal function. In this particular study for example, attainment of diastolic pressure <90 was associated with a significant reduction in mortality and the azotemic deaths were in general in hypertensive patients.

Dean and coworkers performed the first prospective study to analyze renal function in renal artery stenosis. These investigators performed serial renal function tests on 41 patients with documented renal artery stenosis and who had been randomized to medical vs. surgical management. Based on assessment of renal size, PCr, and isotopically determined GFR, 35% of patients had a 10-35% reduction in renal size and 20% of patients had a 50-100% increase in PCr over a mean period of 36 months (Dean 1981). Am important finding in this study is that blood pressure control did not correlate with deterioration of renal function and significant worsening of renal function occured in number of patients whose blood pressure was extremely well controlled. The more convincing result of ischemic nephropathy is that of Dean and coworkers who showed deterioration in estimated GFR over time can be stabilized or even reversed by revascularization (Dean 1991).

In another retrospective study by Schreibner (Schreibner 1984), angiographic progression was correlated with clinical progression in 85 patients with atherosclerotic renal artery stenosis. Of a total of 126 renal arteries, 36% demonstrated significant progression. Progression was correlated with initial PCr but not with blood pressure control.

In summary, the pathophysiology of acute reversible renal failure precipitated by hypotension is due to the AII dependence of GFR of patient with bilateral renal artery stenosis or unilateral stenosis in a functionally solitary kidney. The pathogenesis of chronic ischemic nephropathy is unclear. Experimetntal data on pathophysiology is very sparse indeed. However, the clinical data on the existence of this entity is quite convincing supporting the notion that chronic reduction in renal perfusion per se can lead to loss of renal function independent of hypertensive nephrosclerosis.

Asymptomatic renal vascular disease: a new entity

There has never been a population-based study of the prevalence of renovascular disease. Such as study would not have been feasible due to the low incidence of the disease and the invasive nature of the diagnostic test. The existing estimates of the prevalence are derived from autopsy series and angiography cases series obtained for evaluation of peripheral vascular, coronary or aortic diseases. Although angiographic

case series are biased towards a high incidence of renal artery stenosis, they do clearly document the existence of asymptomatic lesions.

Swartz and White examined for the incidence of renal artery stenosis in unselected autopsy patients and found that the incidence of severe renal artery stenosis increases with age (Swartz 1964):

Age	% with severe stenosis
<64	5%
65-74	18%
>75	42%

Although this was a truly unselected study, patients records of hypertension and renal insufficiency were not fully accessible. The second autopsy series was from Holley and coworkers (Holley 1964) who performed angiograms on cadavers and found 17% incidence of renal artery stenosis on 256 normotensive patients and 56% incidence on 39 hypertensive patients. This study was the first to document renal artery stenosis in normotensive individuals.

Autopsy studies frequently suffer from lack of adequate premortem patient information. Although angiographic studies are highly biased towards high incidences, the clinical records are more reliable. As we cited earlier, the first angiographic study was by Eyler and coworkers who reported the prevalence of critical renal artery stenosis in 500 patients subjected to aortography (Eyler 1962). They found an incidence of 45% in normotensive patients and 67% in hypertensive patients. Valentine and coworkers at Southwestern performed a retrospective analysis of aortograms performed for suspected aorto-iliac or lower extremity vascular diseases and found unexpected severe renal artery stenosis (defined as >50% diameter loss) in 28% of patients (Valentine 1993). Of all the study patients, 41% were normotensive and 59% was described to have mild to moderate hypertension with none having severe hypertension. The incidence of renal artery stenosis was 35% in hypertensive patients and 18% in normotensive patients. Of the 156 patients where PCr was available, 24% had PCr greater than 1.5 mg/dl with no patients in any end stage renal failure programs. Patients with mild renal insufficinecy had 57% incidence of renal artery stenosis while patients with normal renal function had 13% incidence of renal artery stenosis. In prospective study of 100 patients who were referred for intermittent claudication, Choudhri et al showed an overall incidence of 42% renal artery stenosis (>50% reduction of diameter) with 57% of the lesions being bilateral (Choudhri 1992). The incidence of hypertension and renal insufficiency are shown.

Patient characteristic		Angiographic findings			
BP	Normal	>50%	<50%	Bilat	Occluded
N n=38	37%	16%	15%	23%	10%
↑ n=62	47%	18%	5%	26%	3%
S_{Cr}					
N n=53	42%	23%	13%	23%	0%
↑ n=30	33%	17%	7%	23%	20%

In a similar study in 1321 patients undergoing cardiac catherization also underwent renla angiography and 30% were found to have renal artery stenosis with half of the patients having lesions of 50% or greater (Harding 1992). However 47% of these patients were not hypertensive. The most prominant feature in these patients were generalized atherosclerosis. Only 15% of patients with renal artery stenosis had normal coronary or peripheral arteries (Harding 1992).

In summary, both autopsy and angiographic series suggest that critical renal artery stenosis is relatively uncommon in middle age individuals. However, in elderly individuals who has occlusive vascular disease elsewhere, renal artery stenosis is quite prevalent. Frequently, these patients do not have either hypertension or renal insufficiency.

Natural history of renal artery stenosis

The natural course of fibromuscular dysplasia needs to be considered separately from atherosclerotic disease.

I. Natural course of FMD

The fibromuscular dysplasias can be divided into 4 histologic types (Harrison 1971, Pickering 1990). The 4 histologic classes can be divided into 3 radiologic classes since most of them can be distinguished with fairly accurately on angiography.

Intimal Fibroplasia

This is a circumferential deposit of collagen inside in lamina elastica interna. This disease is diagnosed angiographically as a smooth linear focal stenosis in the

midportion of the vessel. When occurring in a child or a young adult, this appearance is pathognomonic for intimal fibroplasia. It accounts for 5-10% of fibromuscular dysplasia's and is equally common in males and females. In the elderly patient, one sometimes can see a smooth looking atheroma that resembles this lesion. Intimal fibroplasia almost invariably progress. Disruption and duplication of the internal elastic lamina leads to dissecting hematomata. This is the entity that has a propensity to spontaneously dissect or thrombose causing acute renal failure. The decision to treat this type of lesion is therefore not difficult.

Fibromuscular hyperplasia

This is a very rare lesion accounting for 2-5% of fibromscular dysplasia characterized by true hyperplasia of smooth muscle and fibrous tissue. It is equally common in males and females. It encroaches on the lumen producing an angiographic picture indistinguishable from that of intimal fibroplasia. It occurs mostly in children and is invariably progressive. Total occlusion is common. Again, treatment is always indicated.

Medial fibroplasia

This is the commonest lesion accounting for 80% of the fibromuscular dysplasias. Because of that, sometime medial fibroplasiais used interchangeably with fibromuscular dysplasia but that is incorrect. The internal elastic mambrane is focally thinned or lost. Muscle is replaced by collagen in the alternating thickened areas. This lesion is characterized by a series of fibrous rings interupted by aneurysmal dilatations. This creates the classical "string of beads" apperance on angiogram. Note that in this lesion, the diameter of the aneurysms exceeds that of the true arterial lumen. Extensive collaterals seen in some cases of atherosclerotic diseases are not described in this disease. Functionally, it may indicate that there is relatively mild ischemia. This lesion is commonly seen in women from age 20-50 and classically affects the middle to distal third, a location quite amenable to dilation.

In a study by Cragg and coworkers (Cragg 1989), they found 71 potential living related donors had fibromuscular dysplasia, these authors managed to obtain informtion on 30 of these patients ended up not donating their kidneys. Although all of them were normotensive at the time of the donor evaluation, 8 (26.6%) of them had developed hypertension after 7.5 years of mean follow-up. Schreibner and coworkers has followed 66 patients for a mean interval of 45 months and observed angiographic progression in 22, or a third of the patients (Schreibner 1984, 1989). Contrary to previous reports of stable medial fibroplasia in patients older than 40 (Meaney 1968), Schreibner found a similar incidence of progression in both young and old patients. During the mean period of 45 months, no complete occlusion were observed despite a few fairly high grade stenoses. Interestingly, despite the angiographic progression, increases in serum creatinine and reduction of renal size was distinctly uncommon. Although this lesion definitely can cause renovascular hypertension, it is unclear how prevalent is ischemic nephropathy in these patients.

Perimedial or subadventitial fibroplasia

This lesion is tightly stenotic with dense collagen within intact adventitia enveloping the lumen for variable lengths. It accounts for 10-15% of fibromuscular dysplasias and has been described almost exclsusively in women. Angiographically, one also sees beading but the size of the "beads" do not exceed the inner diameter of the vessel because of the intact adventitia. This lesion frequently is very tight and there are often reports of severe hypertension in these patients. Risk of thrombosis and dissection although not as common as intimal fibroplasia, the risk is definite. In addition, progresssion to obstruction is common.

In cases of atherosclerosis, deterioration of angiographic and renal function has repeatedly been shown in retrospective as well as prospective studies. The challenging question is how to predict which patients are at risk of progression and who beneifits most from revascularization.

Natural course of renovascular atherosclerosis

Since all patients with hypertension have received medical treatment of some sort, there are no studies documenting the true "natural course" of untreated renovascular stenosis. The only data available on "untreated disease" is on patients with asymptomatic renal artery stenosis. However, the natural course of asymptomatic patients likely differ significantly from and are more benign than those with renovascular hypertension and or renal insufficiency.

Wollenweber and coworkers complied the first large series of 109 patients with renal artery stenosis and found 15% of the patients were azotemic at presentation and over a mean follow-up period of 43 months another 12% developed azotemia (Wollenweber 1968). An additional 20% of patients had worsening of renal function as assessed by ClCr, IVP, isotope scan and kidney size although their plasma values did not reach the defined azotemic levels. Anatomically, 30 patients had repeat angiograms after a follow-up period of 31-74 months. Occlusive disease deteriorated in 21 arteries and new significant stenosis developed in 3 new arteries. The estimated 5 years survival for the 109 study patients was 67%.

Schreibner and coworkers performed a key study defining the natural progression of atherosclerotic renal artery stenosis with serial angiograms and correlated the changes to the clinical status of 85 patients treated medically (Schreibner 1984). Over a mean follow-up period of 52 months, 36% of renal arteries showed significant progression.

% stenosis at presentation		% stenosis at follow-up			
	n	<50%	50-75%	75-99%	100%
<50%	*78*	*54*	12	8	4
50-75%	*30*		*16*	11	3
75-99%	*18*			*11*	7

Angiographic progression was correlated with rise in serum creatinine and decrease in renal size. Interestingly, as we have mentioned above, blood pressure control did not correlate with progression. The most important point to emphasize in this study is that although angiographic progression is overall correlated with clincal progression in the whole study population, it is not true for individual patients. Note the following findings.

Clinical features	Angiographic features	
	No progression n=48	Progression n=37
S_{Cr}		
No change	75%	46%
Increased	25%	54%
Kidney size		
No change	73%	30%
Decreased	27%	70%
Blood pressure		
Well controlled	73%	59%
Poorly controlled	27%	41%

Given this data, it is very difficult to predict for a given patient whether he or she will progress.

As noted earlier, Dean and coworkers prospectively analysed serial anatomic as well as functional changes in 41 patients with atherosclerotic renovascular disease treated medically (Dean 1981). Over a mean follow-up period of 36 months on medical therapy, 37% of patients had a >10% reduction in renal length, 50% of patients had an increase in serum creatinine, and 33% of patients had a >25% decrease in

isotopically measured GFR. Of the patients with significant loss of renal function, a majority of them had blood pressure control that was deemed adequate.

Once a patient reach end stage renal failure with renovascular disease, the prognosis is highly unfavorable. This point has been emphasized by Mailloux and coworkers (Mailloux 1988, Mailloux 1994). First, one needs to recognize that the life expectancy for any dialysis patient at this age group is not great.

Expected remaining lifetime in years for a 60 year old with specific diagnoses are shown:

General population	21.6
Prostate cancer	13.0
Colon cancer	8.0
ESRD	4.3
Lung cancer	2.5

Furthermore, within the dialysis population, Mailloux and coworkers initially subdivided the survival curves into causes of end stage renal disease and noted that the group that did the poorest were those with renovascular disease. Five year survival was dismal 5 10% (Mailloux 1988). Although a more recent report cited slightly a slightly more favorable figure of 18%, it is still extremely low. A large part of this mortality is due to co-morbid conditions like cerebrovascular, peripheral vascular, and coronary artery diseases. If co-morbidity is indeed responsible for a large part of the mortality, then one would expect revascularization and prevention or reversal of renal failure to not have a significant impact on patient survival. This type of long term prospective data is not available. Intuitively, the recurrent problems with vascular access, infections and dialysis associated hypotension most likely contributed to the mortality independently. The retrospective data of Dean and coworkers (Dean 1984) supports but do not prove this point. When all their patients who were selected for aand underwent surgery were compared, those who responded to surgery and stayed off dialysis lived much longer than those who progressed to end stage renal failure despite revascularization.

DIAGNOSTIC APPROACH TO THE PATIENT

In general, investigations can be classified into three groups for different purposes. Screening tests, diagnostic tests, and prognostic tests. Prognostic tests pertain to the ability to predict outcome of intervention. There is an enormous amount of literature on the subject. If one were to summarize it bluntly, one can say that there are no good screening tests and there are no good prognostic test for renal vascular disease. For diagnosis, we have a 100% sensitive and specific gold standard which is angiography.

CLINICAL SCREEN

There are always problems with studies defining clinical criteria to diagnose renovascular disease.

1. Retrospective studies are probably the worst design to look at prediction criteria.
2. Small sample size.
3. Studies performed in referral population that already has a high prevalence of renovascular hypertension will not have the same positive and negative predictive values in the general popuplation.
4. Definition of disease renovascular stenosis or renovascular hypertension.

Granted there are caveats in the clinical screen, it remains the most practical and powerful first line approach to renal vascular disease.
Pooling data from a number of studies, the following clinical clues can be used (Maxwell 1972, Simon 1972, Davies 1979).

Abdominal or flank bruit
Vascular diseases elsewhere

Age of onset of hypertension <25 or >45
Onset of hypertension within last 2 years
Refractory or difficult to control hypertension
Accelerated or malignant hypertension
Grade III or IV retinopathy

Acute renal failure precipitated by sudden fall in blood pressure or volume depletion
Progressive azotemia in a patient with refractory hypertension
Progressive azotemia in a patient with known renovascular stenosis treated medically
Unexplained progressive azotemia in elderly patient or vasculopath

Abdominal or flank bruit remains as the most powerful finding. Grim and coworkers at Indiana studied patients with renovascular hypertension defined by favorable response to surgical revascularization and compared them to patients with primary hypertension and normal controls (Grim 1979). The presence of a systolic and diastolic bruit gave positive predictive values of 67% if the prevalence of the disease is 5%. Of in the right population, abdominal and flank bruits can be heard in 20% of patients without renal artery stenosis (Eipper 1976). In Svetkey's study, a set of clinical criteria not unlike this one were applied to a general population with a predicted prevalence of renovascular hypertension of 5% and defined a subpopulation with a prevalence of 18% (Svetkey 1989, 1990). The highest correlation between selection criteria and and presence of renal artery stenosis was abdominal or flank bruit with an odds ratio of 11.6.

These findings cannot be generated to the population at large. Each of these findings has alternative explanations and should serve only as guidelines to decide whether further testing is neccessary. Different groups have reported different results using clinical screening detecting renvascular disease with positive predictive values from 15% up to 50%.

In summary, clinical clues are important because they dictate all subsequents tests.It should be stressed that these are not dignostic criteria, they are merely situations where one should start thinking. The truth is that the majority of patients with these characterizrics are still not going to have renovascular hypertension.

RENAL SCAN

This is probably the most frequently ordered test for renovascular hypertension. Some excellent reviews have been published (Distler 1991, Nally 1992, Tlchinsky 1993, Pederson 1994) which contain concise summaries of a massive amount of clinical literature.

Glomerular vs. tubular agent

In general there are two groups of agents one can use for renal scans. The so-called glomerular agents, the prototype being DTPA (diethylenetriaminepentaacetic acid), is circulated in the plasma 97% unbound and filtered freely at the glomerulus. Historically, DTPA was used for measurement of GFR. DTPA renal clearance closely resembles that of and usually is a few percent lower than inulin (Klopper 1971, Braren 1979). ^{99m}Tc-labelled DTPA remains the agent of choice because of the high quality images produced by ^{99m}Tc and the low dose of readiation delivered to the patient. ^{131}I-OIH (orthoiodohippuran), similar to PAH (para-aminohipurran), is weakly and reversibly protein bound up to about 70%. IOH is extracted about 80% on a single pass through the kidney and is 20% cleared by the glomerulus and 80% secreted by the proximal tubule (Schwartz 1961). The drawback of this agent is the poorer quality of images and the much higher dose required posing dangers of thyroidal irradiation. In addition to its scintigraphic and dosimetric disadvantages, because OIH clearance parallels renal plasma flow more than glomerular filtration rate, it is theoretically less sensitive to changes induced by ACE inhibitors. However, because of its tubular secretion, IOH yields reasonable images in ranges of GFR that is way below efficient excretion for DTPA and there fore is invaluable for patients with high baseline serum creatinines. The routine renal scan is done with Tc-99m DTPA. In special cases with high serum creatinine, one can request for I^{131}-OIH. As we shall discuss later, the power of the captopril scan relies heavily on a normal precaptopril renogram, in patients with renal insufficiency, OIH is more likely to produce a normal baseline scan than DTPA and hence will increase the sensitivity of the test (Sfakianakis 1987). An agent that has generated some encouraging results is ^{99m}Tc-MAG$_3$ which is ^{99m}Tc-labelled

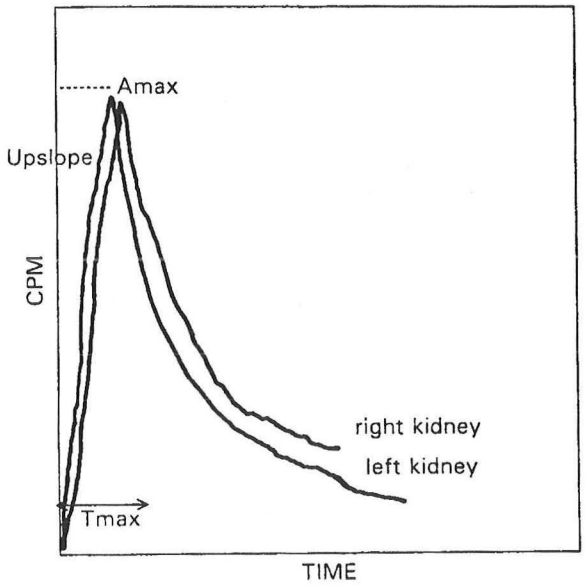
mercaptoacetyltriglycine. This agent combines the imaging and dosimetric advantages of ^{99m}Tc-DTPA with the tubular handlng properties of hippuran derivatives to produce excellent images even in low GFR (Taylor 1991, Dondi 1991). The initial favorable reports await further confirmation.

The renogram

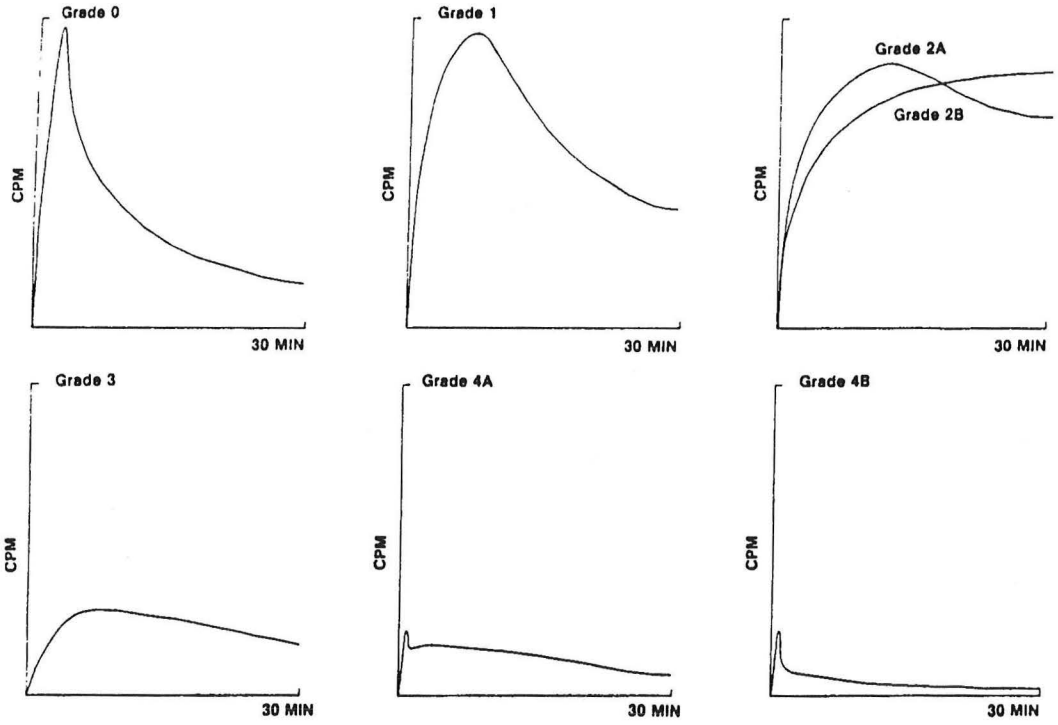
After the isotope is injected into the patient, serial images are obtained over the kidneys. Inspecting the actual scintigraphic dynamic images are important since this allows one to visualize the renal cortex as well as the collecting system and determine the relative contributions of each. It will also show excess motion artefacts from the patient which if present can affect the quality of the interpretation. In addition, if there are functionally important regional perfusion defects from a segmental artery stenosis, it will be apparent on the renal images. Rapid images are obtained over the first minute that constitute the perfusion scan before significant accumulation of isotopes in the tubules. After that, renal extraction and excretion of the isotope begins and that reflect excretory function of the kidney. Background is selected over the aorta or perirenal tissue and the background corrected signal is shown as a time-activity curve as what is called a renogram. The counts are frequently arbitrarily divided into cortex and pelvis. The cortical activity reflects more of extraction and the pelvic activity reflects more of excretory phase.

A normal renogram consist of:

1. Upslope or accretion phase
2. Peak activity (Amax) and the time at which that occurs (Tmax) which normaly is between 3-5 mins.
3. Downslope or excretion phase. A parameter that is sometimes used is the residual cortical activity (RCA) at 20 mins. A normal RCA should be less than 30%.



A normal and some abnormal renograms are depicted schematically on this figure for DTPA. Renograms for OIH are slightly different but the overall pattern is similar. A normal peak should occur between 3 to 5 mins and the isotope should be promptly excreted. Thw abnormalities have been divided into grades (Geyskes 1987, Nally 1991, Oei 1991).



Grade 0: Normal
Grade 1: Uptake rate is slightly reduced, Amax is slightly reduced, Tmax is between 6-11 mins
Grade 2A: Tmax is beyond 11 mins and excretion occurs during 30 min
Grade 2B: Tmax is beyond 11 mins and no excretion in 30 min
Grade 3: Uptake is greatly reduced or abolished

Use of captopril

If one were to bother with a renogram, it should be done pre and post captopril. The much poorer sensitivity and specificity of a single baseline study is really not worth the trouble. The presumed physiologic basis for the captopril scan is derived from animal data with mainly the two kidney one clip Goldblatt model (Ploth 1983, Huang 1983, Nally 1986, Jonker 1992). A dose of 25-50 mg of captopril is given orally and the scan is usually performed in about an hour or two. Some centers perform pre and post scan on the same day while others prefer to do it on seperate days. Opinions vary (1 day to 2 weeks) as to how long on should stop the ACE inhibitor before.

Two points are noteworthy. The power of the captopril scan rest on comparing and detecting differences. Difference between pre and post captopril and difference between the stenosed kidney and the normal one. Therefore, one can imagine that two conditions that will limit the utility if this test is: 1. Bilateral renal artery stenosis and, 2. Abnormal baseline renal scan, the commonest cause being chronic renal insufficiency from any cause.

Nally and coworkers have compiled a set of guidelines mainly for standardization of interpretation of renal captopril scans based on pooled data. (Nally 1991)

Baseline grade	Post captopril grade				
	0	1	2a	2b	3
0	L	H	H	H	H
1	L	I	H	H	H
2a	L	L	I	H	H
2b	L	L	L	I	H
3	L	L	L	I	I

Any change from a completely normal baseline to any grade of abnormality is abnormal and interpreted as "high probability". If the baseline is abnormal, the transition has to be two grades for the scan to be read as "high probability". Any abnormal baseline scans that does not change is read as "indeterminate". Renograms that improve post captopril challenge is felt to be highly unusual for renal artery stenosis and they deserve a "low probability". note that these low and high probability does not carry any numbers in terms or odds ratio and they are in no way the final determinant of the diagnosis. Their diagnostic value will be discussed below.

Use of furosemide

The effect of furosemide as a natriuretic before the scan must be distinguished from the its use as a diuretic during the scan. Effective arterial volume contraction by itself tends to bring about a positive scan due to the high AII levels. If the volume contraction is severe, it may limit increases in renal plasma flow. Although this will increase the sensitivity of the captopril scan but it will greatly decrease its specificity giving rise to a lot of false positive scans. In general, this kind of sensitization should be discouraged because most of the clinical trials that characterize this test were done on patients who were euvolemic. The true value of furosemide has to do with its ability to keep a brisk urine flow. Since its action is in the thick ascending limb, it will not affect isotope handling. Isotope hold-up in the renal pelvis can be normal but the renogram often resembles a grade I defect of renovascular stenosis. The use of

furosemide during the scanning will quickly eliminate the isotope from the renal pelvis if the grade I pattern is due to hold-up. In true renovascular stenosis, furosemide will have minimal or no effect.

As a screening test

Positive predictive value depends on prevalence. For a test with a given sensitivity and specificity, the positive and negative predicitive values depends on the incidence of the disease. Take a hypothetical test with 85% sensitivity and 85% specificity. The prevalence of renovascular hypertension in a referral population or an elderly male population such as the VA may in the range of about 5% although the true prevalence of renovascular hypertension in the general population is more realiztically less than 1%. For a disease prevalence of 5%, a positive result will increase the likelihood of the disease from 5% to 24%, although a nearly 5-fold increase in probability, the absolute likelihood is still low. Further testing must be done on 186 patients. In these, 143 tests will have to be "wasted" to pick up the 43 true positives; or 3.3 negative confirmatory tests for each patient diagnosed. A negative result raises the pre-test likelihood of no disease of 95% to a post-test one of 99%. A small gain indeed.

For a population with a disease prevalence of 30%, a positive test result only doubles the likelihood but it yields a 71% chance of presence of disease. For a disease such as renal artery stenosis, further testing will still have to be done with this kind of probability. However in this instance, 105 negative confirmatory test will be performed to pick up 255 cases; or 0.4 negative confirmatory test per new diagnosis. A negative result decreases the likelihood of the disease from 30% to 7%. A substantial reassurance in a high risk population. The best results from a renal scan as a screening test requires a population with an intermediate clinical likelihood. One can use the clinical clues listed above as warning signs to alert the possible presence of renovascular disease.

As a diagnostic test

The renal scan cannot replace the arteriogram and is not used as a diagnostic test

As a prognostic test

The most important use of captopril renography is in prediction of outcome from revascularization, several major papers are summarized below. All of these papers studied high prevalence population and used rigid criteria of blood pressure response to either surgery or angioplasty as definition of renovascular hypertension.

	n	sen	spec	PV(+)	PV(-)
Fommei 1991	56	93	66	88	76
Setaro 1991	40	80	85	84	80
Geyskes 1991	77	91	68	89	72
Meier 1990	16	86	78	75	88

Serial studies such as the one by Pederson and coworkers, correlated the the normalization of the captopril scan very nicely with the clinical response to revascularization (Pederson 1992).

In summary, captopril renography can be a useful screening test in high prevalence (~30%) patient population. Angiography will still have to be performed in patients with positive scans. Baseline renal insufficiency and bilaterla renal artery stenosis decreases the power of the test. The most important use of this tet is in predicting outcome to revascularization. With the positive and negative predictive values in the literature, it cannot function as the only decision making test but it can persuade either direction in the decision making process.

DUPLEX DOPPLER

Duplex Doppler of renal arteries has received a lot of attention in the last few years. Thus far, there is no data to suggest that Doppler has any role in predicting patient response to revascularization. As a diagnostic test, it may be coming closer to the angiogram with improvement of techniques but it will not replace the gold standard in a long time. The only potential utility of the duplex Doppler is as a screening test.

Technically, this is a rather challenging procedure. But the literature shows that experience centers are obtaining very promising results. A lot of criteria has been devised to detect renal artery stenosis. A lot of these are derived from carotid and femoral Doppler studies. However, because renal arteries are situated so deep, more strigent criteria are frequently mandated which may decrease its sensitivity. Peak systolic velocity of 180 cm/sec or greater has been accepted by many as a useful cutoff. Peak systolic volecities tends to overestimate due to high angle of incidence. In carotid arteries, ratio between prestenotic and stenotic velocities are highly useful. In atherosclerotic renal arteries, because of high incidence of ostial lesions, most of the time it is impossible to obtain proximal velocity. Renal to aortic ratio is used instead (>3.5 significant). Other criteria include absent diastolic velocity, broad band Doppler frequencies denoting post stenotic turbulance, total absence of signal reflective of occlusion. The sonographer would take readings along the renal artery to look for changes such as the ones described. The two recent studies from Winston-Salem and Seattle reported very promising results. According to their studies using the arteriogram as a gold standard, the following results were published.

	(Hansen 1990)		(Strandness 1994)
	Arteries		
	Single	Multiple	Single
Sensitivity	93%	67%	95%
Specificity	98%	100%	90%
PV (+)	98%	100%	98%
PV (-)	94%	79%	75%

Although the criteria were a little different in these two studies, overall excellent correlation with arteriography was found. Several points are noteworthy. First of all, these studies were performed on populations with extremely high pre-test probability of RAS. Application of the same technique by the same investigatiors to the general population will yield much lower positive predictive values. Inadequate study was reported in 4% or less of patients. This figure is probably not realistic for most centers where they do not have sonographers who spent the last seven years doing this procedure. A more realistic figure for the current status of the test will be 10-15% failure rate. Lastly, this is a very time consuming, tedious, and operator dependent procedure. It is difficult enough to find the renal artery, not to mention staying on the signal and walking the length of the renal artery. Expertise outside the few pioneering centers currenty are limited.

A more practical use of the Doppler is in waveform rather than velocity analysis. Indirect Doppler findings of RAS are detectable in regions remotely distal to the site of actual stenosis. In these studies, instead of searching for the deep seated renal arteries, the kidneys are quickly located by conventional sonography and color Doppler is used to identify the segmental and interlobar blood vessels. Then using the color guidance, vessels are located and the waveforms are identified and analyzed. The most significant abnormal waveform pattern is that of tardus parvus which is paraphrased from the peripheral pulse contour of aortic stenosis. Parameters such as acceleration time and acceleration index of the early systolic peak can be quantified. This method is relatively fast and technically not as difficult as mapping out stenoses with peak systolic velocities. A false positive of this method is that diffuse vascular disease can also produce abnormal waveforms and those patients may not have surgically bypassable disease. A false negative of this method is seen in patients with chronic atherosclerotic disease with distal vessels perfused by extensive collaterals giving rise to much less severe wave profiles then that expected from the stenosis in the main renal artery.

One potential use of the Doppler is the possibility of measuring vascular resistance in the cortical arterioles. Such an application can lend itself to the pre and post ACE inhibitor studies measurements of resistance and may have the same

efficacy as the captopril renal scan. This type of application still awaits further study.

In summary, duplex Doppler is promising and may prove in the future to be the screening test of choice. In the general population, with the present sensitivities and specificities, the duplex Doppler will still lead to a considerable amount of normal angiograms. There is no dat thus far to suggest ot can be used as a prognostic test. Technical difficulty is a small hurdle. Although a good test can be and should be learned by all sonographer, the present velociity based procedures are too time consuming to be applied to the large number of patients with hypertenison in the commuity. Waveform analysis simplfies the procedure at the expense of losing some sensitivity.

RENAL VEIN RENINS

There is a vast body of literature on the use of renal vein renins and the results are very contradictory. This test is way too cumbersome and invasive to be a screening test. And it has no role in defining the arterial side of the renal vasculature and for the trouble and risk of going through selective renal vein catherization, there is no reason why an angiogram cannot be done instead. Therefore it is not a diagnostic test. So like captopril renograms, the only possible role is as a prognostic tool.

The physiology of this test is based again mostly on the two kidney one clip model of Goldblatt hypertension. Assuming hypereninemia is the culprit for the hypertension, then the ischemic kidney should be producing high renin and the contralateral kidney should be maximally suppressed. In this model, hypertension is always relieved by unclipping the ischemic kidney. The rationale therefore this tests is that if one can find a patient that behaves like the two kidney one clip rat, one stands some pretty good odds in fixing the hypertension with revascularization. In reality, the situation is much more complex than that and the test is flawed in many ways. Consider the following factors.

The causal link between renal artery stenosis and hypertension in fibromuscular disease is fairly well establish and the clinician will infrequently doubt the response of blood pressure to revascularization. It is in the atherosclerotic population that one is most in need of a prognostic test. It is also in this condition that human pathophysiology deviates the most from the two kidney one clip model as discussed above. Human renal artery stenosis may resemble more closely the chronic phase of the one kidney one clip where renin is suppressed bilaterally due to presumed volume expansion but hypertension in this instance is still relieved by unclipping the artery. This will lead to a false negative RVR study.

What is measured clinically is renal concentration in venous blood and not renin

production. Woods and Michelas (Woods 1968) back n the 60's unequivocally shown that equal blood flow can lead to changes in renin concentration. If renin production remains unchanged ann vsnous blood flow is decreased, renin concentration will increase. If renin production is what is important (which may not even be true), then renal vein renin concentrations are misleading. This will lead to a false positive study. The method using step up from infrarenal caval blood inconjunction with contralateral suppression does avoid part of this flow dependence problem.

Like the captopril scan, diffuse renal small vessel disease can certainly contribute to enhanced response of renin production by captopril. This is another reason for a false positive study. Lastly, unlike the renogram which collects data over 30 mins, RVR measurements are spot measurements on a hormone whose concentration vary from minute to minute. The amount of noise and incorporated into the measurement has never really been analyzed. This is further complicated by sampling variations from catheter positions and unknown contributions from areas with variable degrees of ischemia. Also at very low levels of renin, the radioimmunoassay is extremely susceptible to errors.

Despite these theoretical caveats, RVRs have been used extensively. There are different ways of obtaininf lateralization, The two most common ones are RVR ratios. Using an arbitrary cut-off point of 1.5:1.0 or 2:1 to indicate lateralization. Marks and Maxwell (Marks 1975) had pointed out the arbitrary nature of this ratio and cautioned that this does take into account of the relationship of RVR's to venacaval renin concentration. Both kidneys maybe hypersecreting renin with one higher than the other. Vascular reconstruction on one side will not eliminate the second source of renin. In the review of Marks and Maxwell (Marks 1975), 62 out of 412 patients with a negative ratio was cured by surgical intervention. Vaughan and others (Vaughan 1973, Pickering 1984) have proposed the use of renin increment from the infrarenal caval blood to indicate the contribution from that particular kidney while at the same time examine whether the contralateral kidney is suppressed in its renin production. Vaughan had stressed the importance of using this ratio in nilateral disease. Although some authors are enthusiastic, others showed data that indicate otherwise (Rappelli 1986). The dispute as to whether RVR ratios or Vaughan ratio are superior is unresolved.

The clinical literature is extremely confusing in this areas. There are studies that showed just about any result possible. For this discussion, I will present data from one prospective study from Duke which I believe is the best study done to evaluate the role of RVR in prognosis of renovascular hypertension (Roubidoux 1991). In this prospective trial, 133 patients suspected of having renovascular hypertension on clinical grounds were studied with captopril stimulated RVRs. RAS was defined by angiography and RVH was defined cure or improvement of blood pressure by revascularization. Of the 133 hypertensive patients, 22 had RAS, of those 20 had RVH, 16 of whom had atherscleros is and 4 had FMD. The captopril stimulated RVR

ratios are shown the following table.

		Captopril stimulated RVR		
Dx	n	<1.5	>1.5	>2.0
RVH	20	7	13	10
RAS without RVH	2	0	2	0
1° HTN withour RAS	111	59	52	30

This yields a sensitivity of 65%, specificity of 52%, PV^+ pf 19% and PV^- of 89%. Note the seven patients with RVH who did not lateralize and both of the patients with RAS and 1° HTN laterized. Most importantly, 82 of the patients with normal angiograms lateralized.

Overall in the literature, sensitivity of the test ranges from 60-80% and specificity ranges from 53-62%. False positives ranges from 19-50% and false negatives from 18-71%. (Marks 1975, Lyons 1983, Thind 1985, Sellars 1985, Luscher 1986, Wise 1988). It is important to point out that there are studies that show results that are more convincing than the one I showed.

In summary, RVRs are another way of evaluating the pathophysiology of the patient's renal artery stenosis in an attempt to predict response to revascularization. The physiologic premise of the test is somewhat flawed and the measurements are subjected to a lot of random variations and systematic artefacts. I believe the positive studies are real and increased renin production does reflect ischemia among other changes. A major problem from empirical observations is the frequent lateralization in patients with primary hypertension rendering a positive result meaningless.

CONSIDERATIONS FOR SURGERY, ANGIOPLASTY, OR MEDICAL THERAPY

In general, when assessing a report on renal artery angioplasty, one must be cautious in identifying what the authors judge as a "response" to therapy. For example, in angioplasty, a response can be defined as an increase in lumen angiographically immediately post-dilation, a fall in gradient post-dilation, an immediate fall in blood pressure, or a sustained fall in blood pressure. Only the later consitute a successful response. Definition of partial responses can be quite arbitrary. In terms of slowing down progression of renal insufficiency, one must be cautious to evaluate the definition of response and what parameters are used to define renal function. In examining revascularization, the fibromuscular dysplastic and atheromatous diseases ought to be considered separately.

Fibromuscular dysplasia

In intimal fibroplasia, perimedial fibroplasia and medial hyperplasia, revascularization is always indicated. First, it is because one is dealing with a curable secondary cause of hypertension. Second, one also faces a life long predisposition to loss of functioning renal mass in a young patient. All three of these entities will eventually progress to complete renal atrophy. For intimal fibroplasia in particular, the high risk of thrombosis and dissection always warrants intervention. The only entity that leaves some room for clinical judgement is medial fibroplasia which comprises 80% of clinical FMD. Although Schreibner's series showed patients with medial fibroplasia have very low incidence of clinical azotemia and no progression to complete occlusion (Schreibner 1984, 1989). One can argue that there is some role for observation if the patient's blood pressure is well controlled. However, this is quite controversial. Even in Schreibner's series, one third of patients did show angiographic progression and in Cragg's series (Cragg 1989), 27% of the initally asymptomatic patients eventually developed hypertension. With these odds, it is reasonable to take the approach of fixing all fibromuscular dysplasias lesion.

In this category, percutaneous transluminal angioplasty (PTA) is the initial approach of choice. First, a lot of FMD lesions are positioned in a perfect place for dilatation in the middle and distal third of the renal artery. Second, long term result with PTA has been excellent and shown to be equally efficacious as renal artery reconstruction. Successful dilation rates are in general in excess of 90%, cure rates are 50-60% and improvement rates of 30-40% with failure rate of 5-10% (Martin 1981, Grim 1981, Tegtmeyer 1982, Sos 1983, Geykes 1983, Flechner 1984, Millan 1985). Restenosis rates in general are less than 5% in 5 years. Operative success rates for FMD are essentially comparable (Ernst 1972, Novick 1977, Stoney 1981). Occasionally, branch artery involvement may render the procedure technically difficult although successful angioplasties are now performed up to second order branches in the hands of competent interventional angiographers. Surgery is reserved for lesions deemed to fail or has failed PTA.

In summary, for documented fibromuscular dysplasia. The treatment of choice should be PTA with surgical revascularization as a back-up. For fibromuscular dysplasia, it is controversial as to whether one can manage FMD lesions medically with close follow up of renal function. Decisions must be tailored to each individual. It is impossible to know without angiography whether the patient has one of the more uncommon but higher risk lesions. My bias is if one needs to do angiography diagnosis, a simultaneous angioplasty adds little morbidity. In general, in young patients where stakes are high, intervention morbidity is low, and cure rates are high

Atherosclerosis

Results of PTA in atherosclerotic renovascular disease has been disappointing compared to FMD. There are several series reporting acceptable results of dilatation of the rather uncommon non-ostial atheromata (Cicuto 1981, Sos 1983, Council on Scientific Affairs 1984, Dean 1987). However, the results of the much more common non-ostial lesions have been poor (Cicuto 1981, Sos 1983, Dean 1987). The results of Sos and coworkers illustrate the point well.

Non-ostial non-occluded lesions	Technical result		Blood pressure result Cured	Improved	Failed
	Success	15	4	9	2
	Failure	5	0	0	5
# patients		20			

Out of 20 patients, overall technical success rate was 75% but only 13 patients, or 65% had a blood pressure response. Compare this to ostial lesions. Ostial lesion are not usually attempted, but of the 5 patients they did tried:

Ostial lesions	Technical result		Blood pressure result Cured	Improved	Failed
	Success	1	0	0	1
	Partial	3	0	0	3
	Failure	1	0	0	1
# patients		5			

Even for the ones that were deemed technically successfully, none of the patients had a blood pressure response to the dilation. Most interventional angiographers will not even attempt to dilate ostial atheromata. For the more common ostial lesion, surgery remains the treatment of choice.

One must constantly remember that these patients have generalized atherosclerosis and invariably are poor surgical candidates. The very discouraging reports of mortaity rates of 12-17% are no longer true (Franklin 1975). The mortality in more recent reports is around 5% (Novick 1981, Novvick 1987, Messina 1992, Bredenberg 1992, Libertino 1992). Coronary artery disease is leading cause of mortality (Franklin 1975, Novick 1981). This is in accordance with the angiographic studies showing the high incidence of co-existing coronary and renal vascular diseasse (Valentine 1993, Harding 1992). One series from the Cleveland clinic reported 51 patients with zero perioperative mortality where all coronary and carotid lesions were

operated on before the renal arteries (Novick 1983). Even when long term results were analyzed post operatively, Dean and coworkers found that cardiovascular disease and in particular myocardial infraction was by far the commonest cause of death in their patients with renovascular disease. This has major implications in the evaluation of patients for renovascular surgery.

The results of surgical revascularization are difficult to assess due to variations in patient selection for surgery, different techniques and expertise in different centers, amd different ways of defining and reporting data. Rimmer and Gennari recently performed a metanalysis on 7 major series and cited the following results (Rimmer 1993 and see reference within).

Total #	Surgical Outcome (BP and/or renal function)			
	Improved	Stable	Worse	Death
352	194 (55%)	108 (31%)	50 (14%)	20 (6%)

Although no direct prospective comparison has been made with angioplasty, these results are obviously superior. Most of these studies have follow-up periods of less than 2 years. Long term evaluation of the surgical results are very difficult because one is dealing with a primarily elderly population with high incidence of co-morbid conditions. Dean and coworkers at Vanderbilt reported the results of 198 patients followed over 20 years (median or mean not given) as follows:

No change	174
Thrombosis	4
Stenosis	10
Aneurysmal dilation	7
False aneurysm	3

One of the most difficut problem in deciding on revascularization is that of salvageability of renal function. Total occlusion does not neccessarily imply irreversible damage. Recall the impressive report of Morris and coworkers from the 60's revascularized and who recovered renla function in 8 patients who were moribund because dialysis was not available (Morris 1962). Libertino and coworkers revascularized 15 patients with occlusion renal arteries with complete nonfunction in the obstructed kidney for unknown duration (Libertino 1980). Blood flow and renal function was restored in 13 patients. Wasser and coworkers operated on 5 patients 1 to 38 days after anuric acute renal failure from bilateral renal artery obstruction and salvaged renal function in all of these patients. Schefft and co-workers pointed out that if kidney size is >9 cm, residual function is present on IVP or isotope scan,

retrograde filling of distal renal arterial tree from collaterals, or renal biopsy of well preserved glomeruli and tubules, reversal of renal failure is possible (Schefft 1980).

In summary, the treatment of atherosclerotic renal vascular disease is more complex than FMD. Results of PTA are not as good as that for FMD and are are dismal for ostial lesions. The results of revascularization is encouraging and it remains as the only therapeutic hope for patients who are losing their renal function despite adequate medical therapy. Renal vascular surgery is still a major operation with significant morbidity and mortality. Co-morbid conditions responsible for the high perioperative deaths may dictate carotid endarterectomy and coronary bypass prior to renal revascularization. When recommending this highly aggressive approach has to be viewed in the light of the expected length and quality of life of the patient. Decisions in this case will definitely need to be individualized.

MEDICAL THERAPY

In the late 60's and 70's, pharmacology of antihypertensives became sophisticated and the number of oral agents proliferated. Around the same time, the Cooperative Study of Renovascular Hypertension cited unacceptably high rates of non-response, morbidity and mortality for revascularization surgery. This led to disenchantment for intervenition the developement of the attitude that detection of renovascular disease is inconsequential and one should just treat the blood pressure. A lot of the exixting clinical data came from this period. In the late 70's and 80's, new surgical data emerged that was much improved compared to the earlier results and angioplasty became available. Now medical therapy is considered as an option for the patient with renovascular disease.

No truly prospective randomized controlled study has been performed comparing medical therapy vs. revascularization procedures. Retrospective data seem to indicate that blood pressure control is not an accurate indicator of progression to end stage renal disease. Shapiro and coworkers pointed out that medically treated patients had more cardiovascular morbidity and mortality (Shapiro 1969). This non-randomized retrospective study along with a number of others simply reflect selection bias of medically ill patients being turned down for surgery. Hunt and coworkers followed 214 patients prospectively for 7 to 14 years (Hunt 1974). Unfortunately, this study was not randomized. Surgery was performed on patients who failed medically therapy potentially selecting out patient with more agressive hypertension. On the other hand, qualification for surgery could easily have selected patients with less severe co-morbid cardiovascular disease. Despite the bias, surgical patient had a mortality of 30% vs. 70% in medical patients. Two other retrospective analyzes have come to similar conclusions (Novick 19844, Pickering 1986).

There is no trial comparing the chronic efficacy of different agents for medical therapy. At this point, one would assume all the usual antihypertensive agents can be used. Theorectically, diurectics may be particularly useful for bilateral disease with volume-dependent hypertension. Knowing the pathophysiology of this disease, excessive volume depletion and hypotension should be avoided. ACE inhibitors deserve separate consideration. In the event of tight bilateral stenosis or unilateral stenosis with a solitary kidney, ACE inihibitors will cause acute renal failure and should not be used chronically. However, most atherosclerotic renovascular disease are bilateral but are usually worse on one side where renal function may also be worse but not nonexistent. Under these circumstances, one usually see a more insidious and milder type of azotemia with ACE inhibitors-induced acute renal failure rather than the classical oliguric acute renal failure classically described. There are a lot patients with renal artery stenosis with two functionaing kidneys who has no change in GFR with ACE inhibitors. This will be the young patient with FMD, or the older patient with bilateral atherosclerotic disease but only hemodynamically important unilaterally. These patients are analogous to the two kidney one clip model and ACE inhibitors are very effective in reducing sytemic blood pressure (Case 1982). The important question is does ACE inhibitors preserve renal function in these patients over long periods. What is visible clinically as a no change in GFR is due to a fall in GFR in the ischemic kidney with a concomittant compensatory rise in GFR in the normal kidney. This as discussed before is the basis for the captopril isotope scan.

What happens chronically is different. On the normal side, one expects the kidney to be relatively protected because glomerular hypertension is prevented by lowered systemic pressure as well as prevention of excessive increments of postglomerular arteriolar resistance and hence glomerular capillary pressure. However, on the stenosed side, the glomerulus may be protected somewhat from pressure damage but this occurs at the expense of much reduced renal blood flow. The net result may or may not be favorable deoneding whether ischemic damage or pressure damage is worse. In the rat teo kidney one clip model, chonic ACE inhibition protected the unclipped kidney from hypertensive nephrosclerosis but the clipped kidney developed sever fibrosis presumably from chronic ischemia (Michel 1986, Grone 1986, Jackson 1990).

In summary, medical therapy of hypertension is in general effective in renovascular disease. However, ishemic nephropathy has been shown to progress despite well controlled blood pressure. Although retrospective studies suggest surgery is superior, prospective randomized controlled data is lacking. My bias is that revascularization does improve outcome of renal disease and maybe even survival. It is well documented that under specific circumstance, ACE inhibitors can precipitate reversible acute renal failure. The use of ACE inhibitors in patients who do not develope acute renal failure on a chronic basis is controversial. While its blood pressure lowering effects are beneficial, ACE inhibitors may worsen ischemia in the kidney with the stenotic artery. Prospective randomized control trials are needed to evaluate the renal

preservation effect of ACE inhibitors compared to other equally potent antihypertensive agents.

PATIENT DISCUSSION and OUTCOME

Patient #1. The young white woman with recent onset of moderate to severe hypertension most likely has fibromuscular dysplasia. She will probably have normal baseline scans and unilateral disease. So this patient is most likely going to have positive captopril scan but least likely to need it for prognosis. Because if she has FMD, she will have over 90% chance of responding to surgery. So the captopril scan really has little prognostic value in this range of pre-test probability. Should one just do an angiogram? One would only do the angiogram if one considers angioplasty. Considering the favorable response of FMD to angioplasty, there is no point to risk endovascular catherization to document the lesion and not treat it at the same time. If this is my patient, I would recommend going straight to angiography to define which type of FMD and attempt to dilate the lesion at the same time. So is there no role at all for the captopril scan in this patient? One possible role is to do a captopril scan pre and post angioplasty. If the pre procedure scan is negative, then it is not very helpful. However, if the patient has a very abnormal precaptopril scan which subsequently normalizes, it can be of value as a noninvasive monitoring test. If this patient comes back in three years with hypertension from a recurrent lesion. If one knows the baseline of the test, a repeat exam may hekp to distinguish whether this recurrent renovascular disease or if the patient is developing primary hypertension. The decision to do this should ne individualized. If the patient does not want an invasive procedure, can one judtify not doing an angiogram. The odds are 80% that this patient has medial fibroplasia and of those over half of them may not progress. If that is the case, close monitor of blood pressure and renal function may suffice. If one elects to take this course, I would recommend a captopril scan at baseline for two reasons. First, a positive scan dissuade the desire and a negative scan may provide some reassurance to take the approach of watchful waiting. The other important reason for doing the captopril scan if the patient declines angiography is that one needs a more sensitive way to follow her renal function other than a serum creatinine. Because of the high likelihood of unilateral disease, she can lose considerable functional renal mass without a change in her bllod pressure and before the clinician can detect a rise in serum creatinine. Serial captopril scans once a year can alert the clinician to possible progression and thus recommend intervention.

It turned out that this patient had an equivocal captopril scan that involved a grade 0 to grade 1 change but furosemide was not used. The angiogram showed a 75% stenosis in the middle third of the right renal artery of the medial fibroplastic type. She did not get dilated at the time but dilation was recommended after the angiogram. She did not like the idea and came the Dallas VA for a second opinion. We

felt that despite the uncertain captopril scan, she will still likely respond to dilation. Indeed she did and I saw her two years post angioplasty and she was normotensive on no medicines.

Patient #2. The second patient had a presentation not unlike the first one. Recent onset of severe hypertension in a young individual. However, severe primary hypertension in quite common in a black man in this age group. Therefore while the last patient may have a clinical probablility of around 50% of having renovascular hypertension, this patient I estimate his chance to be less than 5%. The captopril scan in this instance, because of the low pre-test probability will have quite unsatisfactory positive predictive value. If one were to do angiograms on this type of presentation, there will be a lot of negative angiograms. I would treat and follow this patient carefully and only do angiography if there other clinical clues to indicate renovasular hypertension.

This was done and the patient's hypertension was extremely difficult to control with diastolic pressures between 90-95 on significant doses of 4 mediations. He also had documented deterioration of his retinopathy within a period of 18 months. Because of this difficulty, a decision was made to look for renovascular disease because the clinical likelihood was higher and one was facing imminent failure of medical therapy. An angiogram was done which showed a renal artery lesion. The anatomic dilation was successful. Post angioplasty, his diastolic pressure settled to 85 with no change in his medications. A very modest response if any. One year later, his blood pressure was worse and was brought under control with 5 medications. A repeat angiogram was performed and it should a fully patent renal artery. This patient has severe primary hypertension. He might have had two diseases with a renovascular component to his hypertension but this is an example of the fact that hypertension with a renovascular lesion does not mean renovascular hypertension. Although in this patient, since his control was so difficult, I think it is perfectly reasonable to correct this lesion in the hope that it may help. The prognosis if this patient is poor. This is one of those patients who end up in dialysis before they turn 45.

Patient #3. This is a very difficult problem to address. The clinical presentation is classic for bilateral renal vascular disease probably more severe on one side. His clinical status is highly unstable. In the next year, he will lose more renal function. His hypertension will be harder to control. He will very likely have recurrent life-threatening pulmonary edema. If this patient ends up in a dialysis program, his statistical survival will not exceed much more than 2 years. In this patient, revascularization remains the only hope of survival. However, renal artery bypass is a daunting endeavor in this patient. He will need cardiac evaluation including coronary angiograms. Surgery may have to be a two stage bilateral renal artery bypass. There may even be a coronary bypass prior to renal revascularization. Keep in mind that there are no prospective studies showing survival advantages with surgical treatment. In situations such as this one, ne needs to gather all information and present them

frankly to the patient. Tests such as captopril scan may help in predicting outcome. An angiogram should only be performed if the medical and surgical team as well as the patient feels revascularization is worthwhile. If a non ostial lesion is present, an attempt in PTA wil be reasonable. Decisions in these cases will definitely be individualized.

This patient had a captopril scan which was very abnormal at baseline that was worse on the right than the left. The post captopril renogram became grossly abnormal on both sides. The patient actually had a transient rise in S_{Cr} from a single dose of captopril. The patient decided to pursue revascularization and had a combined coronary and renal angiogram. The renal angiogram showed a 90% stenosis on the right with collaterals and a 5% stenosis on the left side; all compatible with the sonogram and renogram findings. Unfortunately, the distal vasculature is extremely poor and his disease was not bypassable. The patient is currently still on medical therapy.

Patient #4. There is no data to guide us in managing this patient. For all practical purposes, this patient may continue to have normal blood pressure and normal renal function for the rest of his life. One can do a captopril scan to assess if the lesion is "hemodynamically significant". One must keep in mind that there is no data to indicate that a positive captopril scan predicts progression. However, one can folow this patient with serial captopril scans which may detect loss of renal function before changes in S_{Cr}.

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