Medical Considerations in the Evaluation of the Obstructed Renal Artery

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Case Presentations

1. WC, 52 y.o. diabetic white male with a chief complaint of claudication in the right leg and occassional rest pain. Serum creatinine was 1.1 mg% and BP was controlled on 80 mg per day of Inderal. Arteriography revealed a totally occluded right common iliac and 80% stenosis of the right renal artery.

2. VS, 57 y.o. white male, mild hypertension (BP 140/90 on a diuretic and atenolol) had a renal scan which showed absent function on the left. Arteriography showed a 8.5 cm left kidney, a 16 cm right kidney and complete occlusion of the left renal artery. He had renal vein studies performed which showed lateralizing secretion (40.8 ng/ml/hr from the left and 9.7 ng/ml/hr from the right). Preop creatinine was 1.4 mg%.

3. AB, 59 y.o. black male, hypertensive for an unknown length of time. Had BP usually easy to control; however, had several episodes of "flash" pulmonary edema accompanied by sharp elevations of BP (200/120). It was not clear whether or not the episodes were preceded by or simply accompanied by hypertension. BUN was 34 mg%, creatinine 2.4 mg%. Arteriogram showed 98% occlusion of the right renal artery and 80% occlusion of the left renal artery. Renal scan showed 55% of function from the right, and 45% from the left. Renal vein renins were planned, but concelled when vascular surgery said this man needed an operation for salvage of the right kidney irrespective of renins.

In recent years there has been a growing recognition that renal artery occlusive lesions may be an important cause of end stage renal disease (ESRD). It has been appreciated and accepted for decades that renal artery lesions may produce hypertension, mimicking the laboratory experiments of Goldblatt (1). However, the fact that occlusive renal artery disease may cause a syndrome of chronic ischemia, and ultimately of renal failure, has been generally unappreciated. This review focuses on the issue of progressive occlusive disease of the renal artery as a factor causing renal failure, and explores several strategies used in the diagnosis and treatment of occlusive disease.

I. Incidence of Occlusive Disease of the Renal Artery.

The precise incidence of occlusive vascular disease as the primary etiology of ESRD in the U.S. is unknown. However, Jacobson has estimated that between 3000 and 6000 new ESRD patients in the U.S. have occlusive vascular disease as the cause (2). Jacobson further estimates that between 60,000 and 120,000 patients in the U.S. have progressive azotemia because of vascular disease. A systematic, prospective investigation of the problem is needed to determine the actual incidence of the problem, and this has not been done.

In one recent prospective British study performed over an 18 month period, renovascular disease as the etiology for renal failure was actively sought (3). The screening criteria in this study were: renal insufficiency, difficult to control hypertension, asymmetrical kidneys, and unexplained renal failure or systemic vascular disease. Ten patients with renovascular disease were identified, and all underwent formal arteriography or digital subtraction angiography. During the period when these 10 patients were identified, 64 new ESRD patients were accepted for renal replacement therapy. Of these 64, 29 patients were over 50 years of age. Several features of these patients are shown in Table 1.

Table 1. Characteristics of 10 Patients with Renovascular Disease as the cause of ESRD (Ref. 3).

x AGE:	65.2
SMOKING HX:	9/10
ON CAPTOPRIL:	5/10
BILATERAL RAS*:	4/10
UNILATERAL RAS, CONTRALATERAL OCCLUSION:	5/10
GENERALIZED ATHEROSCLEROSIS:	5/10

*RAS = Renal artery stenosis

Dispositions in these 10 patients are shown in Table 2.

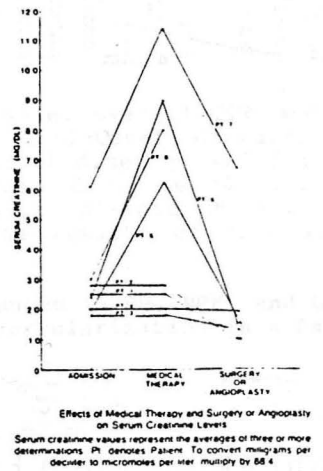
Table 2. Dispositions in 10 Patients with Renovascular Disease as a Cause of ESRD

- 4 PATIENTS WERE UNSUITABLE FOR ANGIOPLASTY/REVASCULARIZATION
- PCTA IN 4 PATIENTS:
  - ONE DIED OF MI DURING PROCEDURE
  - ONE UNSUCCESSFUL
  - ONE SUCCESSFUL, BUT NO CHANGE IN RENAL FUNCTION
  - ONE SUCCESSFUL, IMPROVED Cl_{Cr} FROM 23 TO 46 ml/min
- SURGICAL REVASCULARIZATION IN 2 PTS:
  - SPLENO-RENAL PROCEDURE; NO IMPROVEMENT
  - HEPATO-RENAL PROCEDURE; Cl_{Cr} IMPROVED TO 33 ml/min

Thus, renovascular disease was the cause of ESRD in 6% of the entire dialysis and transplantation program, and the cause of ESRD in 14% of patients over 50 years of age. These statistics, although based on a very small sample size, are in generally close agreement with Jacobson's estimates of the problem in the U.S.

The potential reversibility of this occlusive disease has been emphasized in two similar studies. In the first of these, Ying and colleagues surveyed 106 consecutive patients admitted for diagnostic evaluation; of these, 10 patients were found to have hypertension and either bilateral atherosclerotic renovascular disease or unilateral renal artery stenosis in a solitary functioning kidney (4). Medical therapy in the hospital often induced further deterioration in renal function despite good blood pressure control (Figure 1).

Figure 1. Changes in Serum Creatinine with Medical and Surgical Intervention



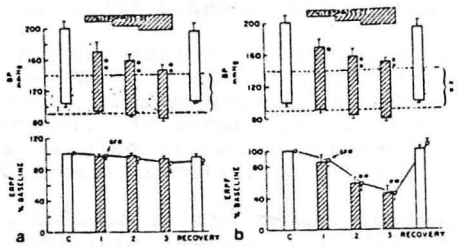
Effects of Medical Therapy and Surgery or Angioplasty on Serum Creatinine Levels

Serum creatinine values represent the averages of three or more determinations. Pt. denotes Patient. To convert milligrams per deciliter to micromoles per liter, multiply by 88.4.

As shown in Figure 1, the serum creatinine was sharply improved by either surgical revascularization or transluminal angioplasty. This study focused attention on the possibility that repair of occlusive renal arterial disease could preserve renal function.

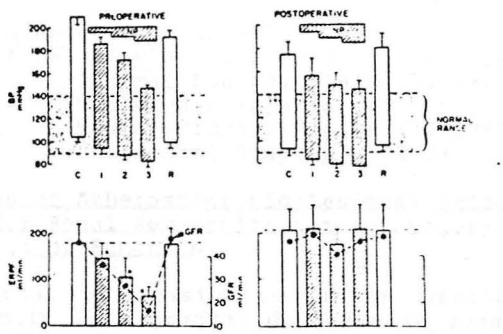
A second study corroborated these findings. In this study, Textor et al (5) studied renal plasma flow (hippurate clearance) and GFR (iothalmate clearance) in 16 hypertensive patients. Eight patients had unilateral renal artery stenosis; eight other patients had bilateral renal artery stenosis. Textor et al lowered blood pressure to normotensive values (see Figure 2, below) in both groups of patients while following RPF and GFR. The results of the first part of the study are summarized in Figure 2:

Figure 2. Changes in BP, RPF, and GFR in 16 Hypertensive Patients



As shown in the figure, overall RPF and GFR were unchanged in the patients with unilateral disease; in contrast, in the patients with bilateral disease, RPF fell from 152 to 66 ml/min as GFR declined from 38 to 16 ml/min. Four of these eight patients with bilateral disease underwent revascularization and were restudied. The results of this experiment are shown in Figure 3.

Figure 3. Changes in BP, RPF, and GFR after Revascularization in 4 Patients



In contrast to the decline in RPF and GFR seen pre-operatively (left panels), the graded reduction in blood pressure post-operatively resulted in no changes in RPF or GFR. Thus, these patients were able to regulate GFR and RPF over a wider range of perfusion pressures.

These two studies focused attention on the importance of fixed (>70%) stenosis of the renal artery as a cause of renal insufficiency. The particularly worrisome feature of this disorder is the tendancy for the lesion to progress over time, often in an insidious, silent manner.

II. Causes of Occlusive Disease of the Renal Artery

The causes of chronic occlusive disease of the renal artery are listed in Table 3. Atherosclerosis typically involves the proximal main renal artery, rarely extending beyond the proximal third of the vessel. In about 75% of cases, significant aortic atherosclerosis is also present. Stenosis of the renal artery due to atherosclerosis is bilateral in about 50% of patients (6).

Arterial fibrodysplasia is the second leading cause of occlusive disease, and dysplastic lesions are classified by which region of the artery is involved. Intimal disease affects primarily infants and young adults. Medial hyperplasia is uncommon, involves the mid-third of the renal artery, and occurs in women 0 to 50 years old. Medial fibrodysplasia is the most common non-atherosclerotic disease causing renal artery occlusion, aggregates in females (9:1 incidence, 25 to 45 years of age), and often involves other arteries; diffuse and peripheral types exist. Perimedial dysplasia is another disease which is most common in women between 30 and 50 years of age, and it appears to be more progressive than medial fibrodysplasia.

Table 3: Causes of Chronic Occlusive Disease

1. Atherosclerosis - 70%
2. Arterial Fibrodysplasia - 20 to 25%
   - Intimal Fibrodysplasia (1-2%)
   - Medial Hyperplasia (<1%)
   - Medial Fibrodysplasia (17-20%)
   - Perimedial Dysplasia (2-3%)

III. Progression of Atherosclerotic Lesions; Selection of Patients for Renal Revascularization Surgery for Preservation of Function.

As recognition that progressive occlusive disease of the renal artery could result in a gradual decrease in renal function has increased, several criteria have been examined to learn what predicts the deterioration of renal function over time. The issue of how rapidly lesions progress was addressed by Schreiber et al (7) and is depicted below in Table 4:

Table 4: Progression of Disease

% STENOSIS INITIALLY	<50	50 to 75	75 to 99	100
1. <50% (n=78)	54 (41)*	12 (36)	8 (51)	4 (59)
2. 50 to 75% (n=30)		16 (29)	11 (34)	3 (23)
3. 75 to 99% (n=18)			11 (21)	7 (13)

*( ) = angiographic interval

This study makes the point that progression of atherosclerotic occlusive disease in common, particularly in higher grade obstruction.

In another aspect of this study, 85 patients with atherosclerosis (51M, 34F, mean age 51.3 yrs) were studied (7). Thirty-one (36%) of the patients had hypertension; the mean angiographic follow-up was 52 months, and the clinical follow up was for 87 months. Several parameters were followed over the angiographic interval of the study; the patients were subdivided into those with progressive renal artery lesions and those without. These comparisons (Table 5) show that BP control did not necessarily correlate with a non-progressive outcome. Serum creatinine change (a 20% increase was defined as deterioration) only roughly predicted progressive disease. The best predictor of those parameters followed was a decrease in renal length (>1.5 cm was considered significant).

Table 5: Predictors of Deterioration in Renal Function

Correlation of Serum Creatinine, Kidney Size, and BP Control With Progression of Atherosclerotic Renal Artery Stenosis

	No Progression (n = 48)	Progression (n = 37)	P
Serum creatinine			
No change	36 (75%)	17 (46%)	< .02
Increased*	12 (25%)	20 (54%)	
Kidney size			
No change	35 (73%)	11 (30%)	< .001
Decreased†	13 (27%)	26 (70%)	
BP control			
Good‡	35 (73%)	22 (59%)	> .3
Poor§	13 (27%)	15 (41%)	

*Greater than 20% increase from initial serum creatinine

†The appearance of a 1.5 cm or greater discrepancy in kidney size

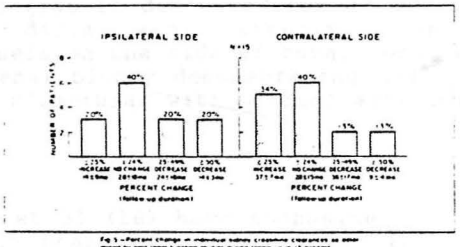
‡Diastolic BP < 100 mm Hg 90% of the time

§Diastolic BP > 100 mm Hg more than 10% of the time

Reproduced with permission from Schreiber et al 18

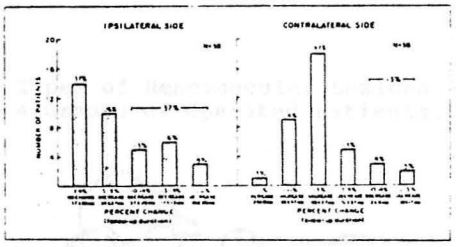
Studies which have examined renal function serially are unusual in this literature, as most reports are follow-ups on technical procedures. Dean et al (9) followed serial renal function in 41 patients with renovascular hypertension secondary to atherosclerosis. These patients had been randomly selected for non-surgical management. In this group, 17 patients had deterioration in renal function despite "adequate" blood pressure control (no specific data given). Changes in individual creatinine clearances are shown below in Figure 4.

Figure 4: % Change in Individual Creatinine Clearances by Split Renal Function Studies



Note that the decreases in creatinine clearances were relatively comparable between the sides; ie., the % undergoing a decrease in renal function (40% ipsilateral vs 26% contralateral) is similar between groups. However, a more striking decrease in renal length (as assessed by IVP's) was voted in the involved kidney (Figure 5).

Figure 5: % Change in Renal Length Over Time in 38 patients



Here a decrease in renal length of $\geq$ 10% ocurred in 13% of contralateral kidneys whereas 37% of ipsilateral kidneys shrunk significantly. Thus, while there is evidence for some deterioration in size in these kidneys managed non-operatively, there is weaker evidence that GFR is adversely affected. Future follow-up studies of this issue should include details on blood pressure control.

Several studies have examined the factors which most reliably predict a successful outcome in renal vascular occlusive disease. These have been recently summarized by Novick (8):

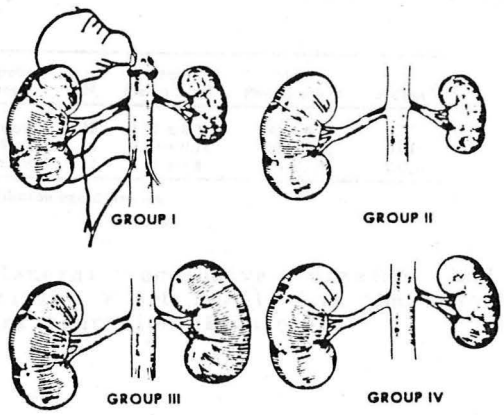
Table 6. Factors Predictive of a Successful Outcome in Vascular Reconstruction.

1. Kidney size > 9.0 cm
2. Function of the involved kidney on intravenous urography or isotope renography
3. Angiographic demonstration of retrograde filling of the distal renal arterial tree from collateral vessels on the side of total renal artery occlusion.
4. A renal biopsy demonstrating well preserved tubules and glomerular with minimal arteriolar sclerosis.

Recently Feltrin et al (10) have emphasized that filling defects on the nephrogram phase of excretory urography best correlates with a poor surgical result. These workers carefully examined the vasculature in extirpated kidneys which exhibited this abnormality and found extensive evidence of irreversible damage. They stress that size alone, function alone, and biopsy alone are all criteria subject to variability and exception.

Several groups have demonstrated revascularization of the kidney for preservation of renal function to be a viable procedure. Novick et al reported on 51 patients with differing anatomy who underwent revascularization procedures (11). The types of lesions present are illustrated in Figure 6:

Figure 6: Types of Renovascular Lesions Present in 4 Groups of Operated Patients.



Group I patients had chronic bilateral arterial occlusion (but good distal run-off); group II patients had arterial stenosis to a solitary functioning kidney; group III patients had bilateral high grade stenosis, and group IV patients had unilateral high grade disease or occlusion in an atrophic kidney. The results of surgery and the length of follow-up are shown in Table 7.

Table 7: Results of Revascularization in 4 Groups of Patients.

Postop. Renal Function	Group I	Group II	Group III	Group IV	Total No. Pts.
Serum creatinine improved:	4	7	11	12	34
Mean preop. mg./dl.	7.06	3.20	2.43	2.31	3.01
Mean postop. mg./dl.	2.15	2.36	1.67	1.58	1.84
Serum creatinine unchanged:	1	4	5	4	14
Mean preop. mg/dl.	6.8	1.96	1.78	2.03	2.26
Mean postop. mg./dl.	7.4	1.83	1.68	1.95	2.21
Serum creatinine increased:		3			3
Mean preop. mg./dl.	0	2.73	0	0	2.73
Mean postop. mg./dl.		3.30			3.30

Overall, improvement occured in two-thirds of patients in the short follow-up period of the study; no control group was included in this study.

Dean et al (12) reported similar success in a revascularization study performed at Vauderbilt. In this study, however, Dean et al disagreed with several general axioms in the management of these patients: 1) renal biopsy to determine viability was not helpful; 2) renal length to exclude kidneys from revascularization was not always warrented; 3) larger, poorly functioning kidneys had the worst prognosis. The most striking improvements in renal function were observed in patients with the worst renal function, as illustrated in Table 8.

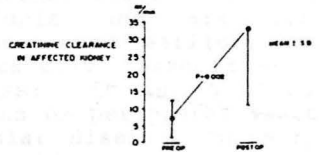
Table 8: Changes in Serum Creatinine after Operation

Pre-operative Group	N	Mean Pre-op ± S.D.	Mean Post-op ± S.D.	p Value*
<2.0 mg/dl	32	1.37 ± 0.32	1.45 ± 0.48	0.37
2.0–2.9 mg/dl	9	2.29 ± 0.28	1.88 ± 0.52	0.051
≥3.0 mg/dl	17	4.85 ± 1.8	3.46 ± 1.9	0.013

* Wilcoxon signed rank test.

Patients with bilateral occlusive disease and moderate azotemia/serum creatinine > 3.0 mg/dl) had the largest fall in serum creatinine after operation (Figure 7).

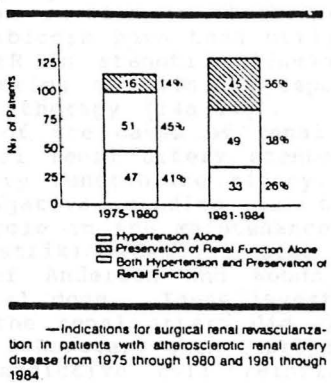
Figure 7: Changes in Creatinine Clearance after Revascularization



Thus, this study would conclude that few criteria are absolute contraindications for revascularization of the kidney for occlusive disease.

As the recognition of occlusive renal artery disease has grown, there has clearly been a major change in the indications for operation in major medical centers in the U.S. As shown in Figure 8, the indications for surgery for preservation of renal function have grown from 14% to 36% of the total number of cases at the Cleveland Clinic. Operation for hypertension alone has declined from 41% to 26% (13).

Figure 8: Indications for Surgical Renal Revascularization 1975 to 1980 and 1981 to 1984.



—Indications for surgical renal revasculanzation in patients with atherosclerotic renal artery disease from 1975 through 1980 and 1981 through 1984

It is also clear that severe azotemia may be sharply reversed by revascularization procedures (14).

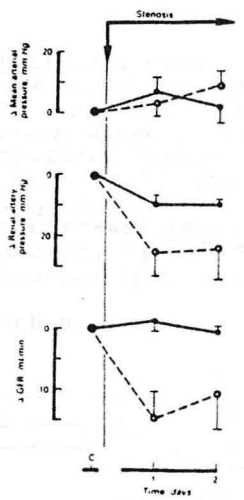
III. Detection of Occlusive Disease of the Renal Artery.

The most common cause of occlusive disease of the renal artery is atherosclerosis. Other causes (Table 3) occur more commonly in younger individuals and are often associated with hypertension. As mentioned earlier, atherosclerosis of the renal artery is usually associated with a generalized atherosclerotic process: it is not uncommon for patients to have symptoms and signs of peripheral vascular disease, coronary artery disease, vascular disease, coronary artery disease, and to have a history of smoking.

Detection of significant occlusive disease of the renal artery has classically depended upon the development or worsening of hypertension in a previously stable individual or on the worsening of renal function. As pointed out earlier in the discussion regarding renal perfusion pressure, the recognition of ischemia to the entire renal mass is precipitated by lowering renal perfusion pressure to normotensive levels (4,5). What distinguishes patients with significant occlusive disease of the renal artery from patients with nephrosclerosis (eg., from malignant hypertension) is that a progressive decline in renal function occurs in the occlusive group, despite goal blood pressure achievement.

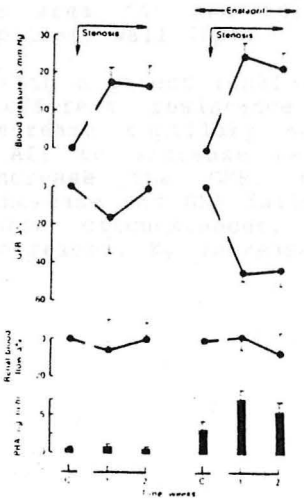
The role of intrarenal angiotension II (AII) in the complex hemodynamic response to partial occlusion of the renal artery has been inferred from studies in which an AII antagonist or converting enzyme inhibitors have been utilized. This role of AII in maintaining GFR in stenotic kidneys initially came to light decause of a series of clinical reports of acute renal failure following CEI therapy (14a-14g). It was subsequently recognized that many of the cases of renal failure occured in patients with bilateral renal artery stenosis or renal artery occlusion in a solitary functioning kidney. The sum of these clinical and investigative studies is that AII plays an important regulatory role in the maintenance of GFR in stenotic kidney lesions. One striking demonstration of this is provided by the experiments of Anderson and Woods (15) performed in chronically instrumental dogs. These investigators showed that an 85% occlusion of the renal artery did not change GFR under control circumstances. However, when captopril was given to the animals and the constrictive cuff reinflated, GFR declined significantly (Figure 9).

Figure 9: Effect of CEI on Acute, Non-Hypertensive Renal Artery Stenosis



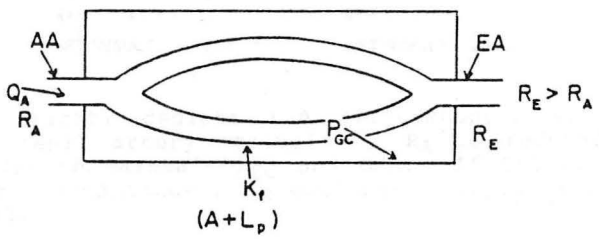
Similar finding were present in the context of chronic stenosis in these animals, as shown in dogs studied after two weeks, with and without converting enzyme inhibition (Figure 10).

Figure 10: Effect of CEI in Chronic Renal Artery Stenosis



The understanding of the pathophysiology in intrarenal AII in syndromes of renal artery occlusion requires some understanding of the determinants of GFR. A brief overview is as follows: the rate of filtrate formation depends upon several variables: plasma flow rate (Q_A), capillary hydrostatic pressure (P_{GC}), afferent arteriolar resistance (R_A), and efferent arteriolar resistance (R_E). In general, the driving force for filtration depends upon P_{GC}, which is the resultant of Q_A; Q_A depends in turn on the relative resistances, R_A and R_E. Several of these factors are illustrated schematically in Figure 11.

Figure 11: Forces which Determine GFR.



Another important factor in the rate of filtrate formation is the ultrafiltration coefficient (K_f), which is the product of the capillary surface area (A) and the intrinsic hydraulic permeability of the capillary wall (Lp).

In the normal kidney with a patent renal artery, AII exerts an effect to increase efferent resistance more than afferent resistance and to decrease capillary surface area (16,17). While the effect of AII to increase R_E more than R_A would increase P_{GC} and increase the GFR, the decrement in A counterbalances this increase and GFR falls. If CEI inhibition is applied under these circumstances, R_E falls, and P_{GC} declines; however A increases, K_f increases, and GFR increases (Figure 12, left).

Figure 12: Determinants of GFR In a Non-Stenotic and Stenotic Kidneys

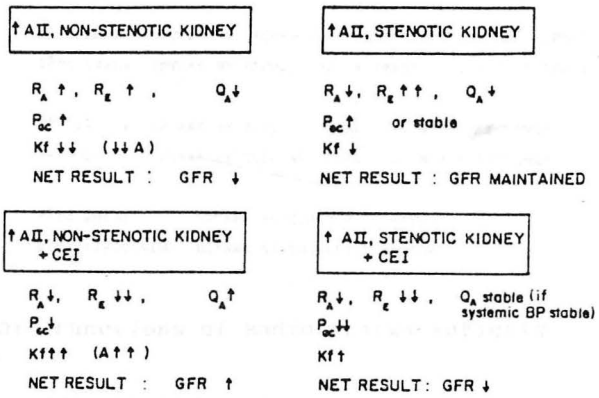


Figure 12 (right) depicts the circumstances surrounding CEI effects in renal artery occlusion. R_A is reduced, and R_E is high in order to maintain P_{GC} and GFR. If CEI is administered under these circumstances, R_E declines sharply, P_{GC} is reduced, and GFR falls.

This decline in GFR in a significantly stenotic kidney has more than theoretical importance and interest. By combining the use of captopril with renal scintography, important diagnostic information has been obtainable in several studies.

Tables 9 and 10 list several features which characterize renal scintography procedures. The most commonly utilized scans are the ^{99}Tc-DTPA scan (which estimates GFR) and ^{131}I-sodium iodohippurate which estimates renal plasma flow.

Table 9a: Renal Scintography: Radio Pharmaceuticals

- ^{51}Cr EDTA (chromium ethylene diamine tetraacetic acid)
- ^{99}Tc DTPA (technetium diethylene triamine pentaacetic acid)
- ^{131}IOIH and ^{123}IOIH (radio labelled orthohippurate)
- ^{99}Tc DMSA (technetium dimercaptosuccinate)
- ^{99}Tc Aprotonin

Table 9b: How Radio Pharmaceuticals Are Removed From Blood

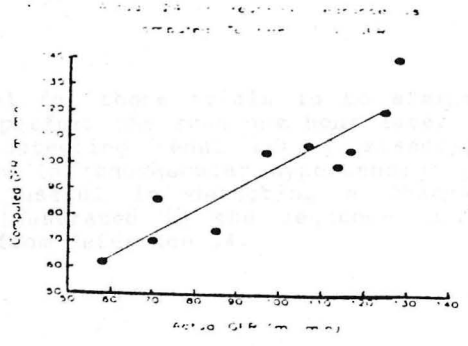
^{51}Cr EDTA:	UPTAKE BY GLOMERULAR FILTRATION, 20% EFFICIENCY
^{99}Tc DTPA:	UPTAKE BY GLOMERULAR FILTRATION, 20% EFFICIENCY
^{99}IOIH :	UPTAKE BY TUBULAR SECRETION, 83% EFFICIENCY
^{123}IOIH :	UPTAKE BY TUBULAR SECRETION, 83% EFFICIENCY
^{99}Tc DMSA:	UPTAKE BY TUBULAR FIXATION
^{99}Tc APROTONIN:	UPTAKE BY TUBULAR FIXATION

Table 10: Functions of Radio Pharmaceuticals

- IOIH YIELDS EFFECTIVE RENAL PLASMA FLOW (ERPF)
- EDTA, DTPA YIELDS GFR
- RENAL CLEARANCE DENOTES MOVEMENT OF A COMPOUND FROM BLOOD TO URINE
- ANY OF THE COMPOUNDS MAY BE USE TO DETERMINE THE CONTRIBUTION OF ONE KIDNEY TO TOTAL KIDNEY FUNCTION- ACCURATE TO WITHIN 6%

Split function renal clearance tests (in which each ureter is catherized and individual clearances are measured) have confirmed (18) that agreement within 6 ml/min exists with ^{99}Tc-DTPA and measured GFR (Figure 13).

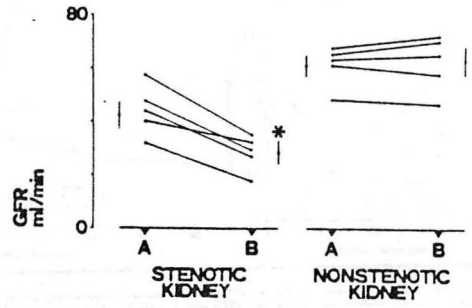
Figure 13: Agreement Between Actual GFR and ^{99}Tc-DTPA Scan



Relationship between 24-hr creatinine clearance and [^{99m}Tc]DTPA GFR in ten patients with EH ($r = 0.913$, $p < 0.001$).

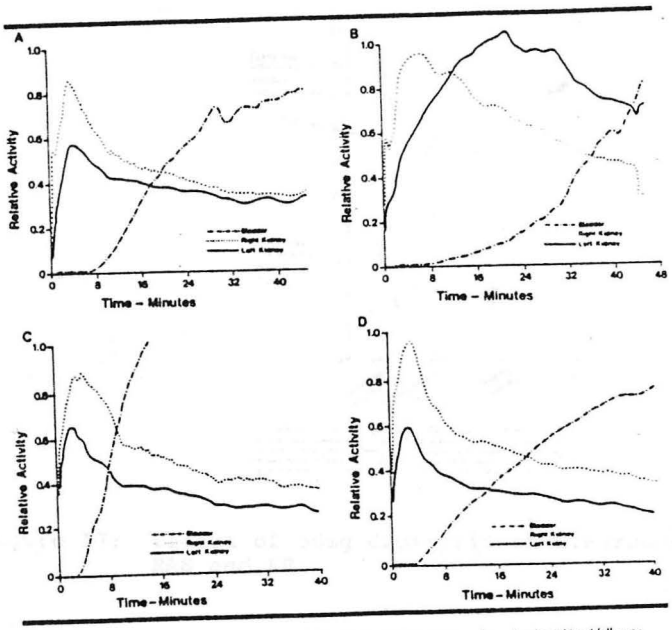
Given the fact that in occlusive renal artery disease the increase in efferent arteriolar tone supports GFR, and since efferent arteriolar tone is, in turn, dependent upon AII, the use of captopril would be expected to induce a decrease in GFR in stenotic kidneys. In fact, this has proven to be the case in several recent studies. In a study by Cuocolo et al (19), captopril induced a decrease in GFR in stenotic kidneys from 42 to 29 ml/min; GFR in non-stenotic kidneys was stable (Figure 14).

Figure 14: Effect of Captopril on GFR in Renal Artery Stenosis



The usual protocol for these trials is to administer captopril 25 mg p.o. and reperform the scan one hour later. This tool has been useful in detecting renal artery stenosis not only in ischemia, but also in renovascular hypertension (20-33). These scans have been useful in detecting a change in GFR non-invasively, as illustrated in the sequence of scans shown in Figure 15 (A-D), from Reference 34.

Figure 15: Changes in GFR in Renal Artery Stenosis



Unilateral renal artery stenosis. Top panel: Tc-99m DTPA time-activity curves during baseline (A) and following captopril stimulation (B) prior to surgery. Bottom panel: Tc-99m DTPA time-activity curves without captopril (C) and during captopril (D) two weeks following left renal angioplasty. See text for details.

The patient illustrated in Figure 15 demonstrated uptake and excretion of DTPA, although peak activity of the left kidney was about two-thirds that of the right (15A). Captopril resulted in marked changes in the DTPA study: prolonged uptake, accumulation, and delayed excretion on the left were consistant with a diagnosis of left renal artery stenosis (15B). Subsequent angiography demonstrated 70% stenosis on the left with two normal right renal arteries. The patient underwent successful percutaneous transluminal renal angioplasty, which normalized blood pressure. Post angioplasty, DTPA studies did not show an alteration in uptake or excretion after captopril (15C and 15D).

These changes in stenotic kidneys are in contradistinction to changes seen post-captopril in essential hypertension (Figure 16 and 17).

Figure 16: Effect of 50mg Captopril Extraction of Na-Hip and I-Thal in RAS and EH.

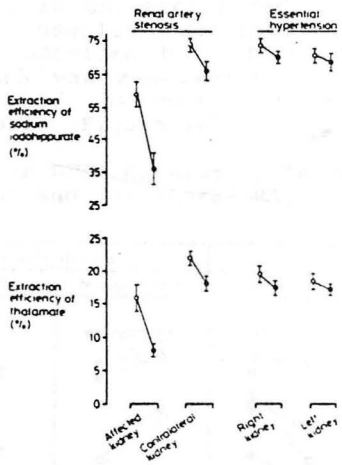
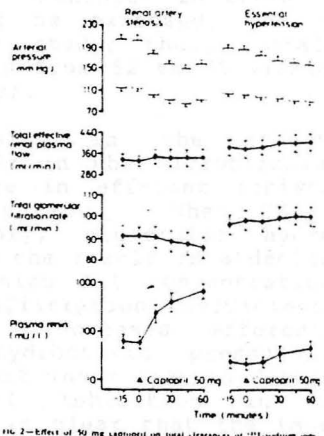
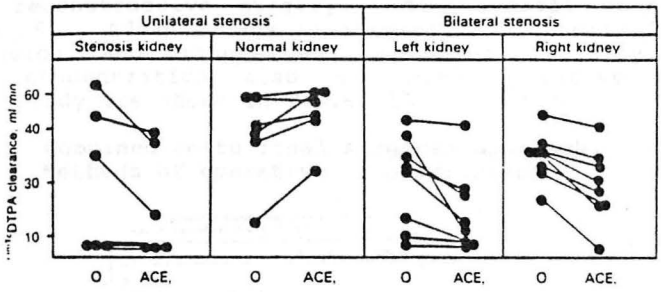


Figure 17: Effect of 50mg Captopril on Clearances in RAS and EH



Notice that GFR decreased in both the stenotic and non-stenotic kidneys in the study by Wenting et al (22, Figure 16). Clearly, the fall in GFR on the stenotic side was greater than on the non-stenotic side. This fall in GFR on the non-stenotic side is not universally seen; in fact, in unilateral renal artery stenosis, overall GFR does not usually decline. The clearest demonstration of this is provided by a study by Johnston and Jackson (18), in which GFR was assessed by split function GFR (^{99}TC-DTPA) in two groups of patients - those with and those without renal artery stenosis (Figure 18).

Figure 18: Changes in DTPA Clearances in Patients with Bilateral and Unilateral RAS.



As can be appreciated in these studies, unilateral RAS resulted in a fall in GFR in only the stenotic kidney; GFR in the normal kidney increased. Hence; overall GFR (and serum creatinine) would be expected to be unchanged in these circumstances. In contrast, and as would be expected, the GFR fell in both stenotic kidneys in the study; thus, overall GFR fell after converting enzyme therapy from 52 to 35 ml/min (and declined in 19 of 22 stenotic kidneys).

As mentioned previously, in the stenotic kidney, the circumstances which exist in the microcirculation are inferred to be a marked increase in efferent resistance and afferent resistance is extremely low. When CEI occurs, efferent resistance falls sharply, glomerular hydrostatic capillary pressure is reduced, and the result is a decline in GFR. In the non-stenotic kidney a high AII concentration decrease plasma flow (Q_A) and the ultrafiltration coefficient (K_f) (which tend to decrease GFR) but increases efferent resistance and glomerular capillary hydrostatic pressure (which tend to increase GFR). Since most investigators demonstrate an increase in GFR following CEI inhibition in the non-stenotic, unobstructed kidney, it is clear that the improvement in Q_A and

the increase in K_f override the decline in R_E and P_{GC}. Should systemic pressure decline precipitously, a fall in Q_A may occur, and GFR may not increase. Other examples of these changes with scans exist in the literature (23-36).

IV. Treatment of Occlusive Renal Artery Disease

As mentioned earlier, the indication for operation in renal artery surgery in changing from hypertension to preservation of renal function (13,37). Successful revascularization of the occluded renal artery had been reported anectodally for years (38-42). Since many patients have combined aortic and renal artery disease the results of the study by Poulias et al (43) are of interest. These workers reported their operative experience in 35 patients who underwent simultaneous aortic and renal artery reconstructive surgery. The overall operative mortalility was 6%. Advanced age (> 65 yrs), an "abnormal" ECG, prior hypertension, and diabetes all increased morbidity. An elevated BUN concentration also increased operative risk. Results of the study are shown in Tables 11 - 14 below.

Table 11: Combined aorto-renal surgical approach. Methods of operative reconstruction

—Combined aorto-renal surgical approach. Methods of operative reconstruction

	No. of pts.	Percent
(A) *Aorta*		
(a) Aortic straight graft	6	17%
(b) Aorto bifemoral graft	29	83%
Total	35	100%
(B) *Renals*		
(a) Bilateral renal artery bypass	7	20%
(b) Unilateral renal artery bypass	28	80%
Total	35	100%

Table 12: Combined aorto-renal surgical approach. Operative indications.

—Combined aorto-renal surgical approach. Operative indications

Pathology	Pts.	Percent
Leriche I with hypertension	14	
Leriche I without hypertension	2	45.7%
Leriche II with hypertension	5	
Leriche II without hypertension	1	17%
Leriche III with hypertension	4	
Leriche III without hypertension	1	14.3%
Abdominal aneurysm with hypertension	4	
Abdominal aneurysm without hypertension	4	23%
Total	35	100%

Table 13: Combined aorto-renal surgical approach. Post-operative results in 25 hypertensive patients

	RESULTS				
Pathology	Pts	Cured	Improved	Unchanged	Death (Operat.)
Leriche I					
With one renal	11	2	7	1	1
With two renals	3	1	2	0	0
Leriche II					
With one renal	4	0	3	1	0
With two renals	1	1	0	0	0
Leriche III					
With one renal	2	0	1	1	0
With two renals	2	1	0	0	1
Abdominal aneurysm					
With one renal	3	0	1	2	0
With two renals	1	1	0	0	0
	27 (100%)	6 (24%)	13 (52%)	6 (24%)	2 (7.4%)
			Total death rate		(5.7%)

Table 14: Combined aorto-renal surgical approach. Evaluation of risk factors in relation to overall mortality

Risk factor	Pts	All deaths	Per cent
Age 60	24	9	37.5%
Hypertension 200	4	1	25%
Tobacco abuse	31	11	35%
Periph. vasc. dis.	9	2	22%
Heart disease	8	2	28%
EKG positive	8	3	37%
Serum creatinine 3 mg dl	4	2	50%
Hyperlipidaemia	18	4	22%
Diabetes	5	1	20%

Hypertension was improved and renal function improved in the operation performed for that indication. It is important to stress that a controlled trial comparing medical therapy to surgical therapy has not been performed. Percutaneous transluminal angioplasty (PTA) has been utilized with increasing frequency to treat the stenotic renal artery and this experience has been recently reviewed by Geyskes (44). As summararized in Table 14, the results are generally reported to be excellent, particularly for fibromuscular disease.

Table 15: Results of PTA

Major Studies Reporting Technical and Antihypertensive Response of Renovascular Hypertension to PTRA. Graded Antihypertensive Response (%) Specified for Fibromuscular Dysplasia and Atheromatous Renal Artery Disease in Patients With a Positive Technical Result (n = No.)

Author	Year of Publication	No. of Patients	Positive Technical Result (%)	Antihypertensive Result: Fibromuscular Dysplasia (Cured (%) + Improved (%) = Total (%))	n	Antihypertensive Result: Atheromatous Disease (Cured (%) + Improved (%) = Total (%))	n	Follow-up Period (mo)
Sos[12]	1983	89	56	59 + 33 = 93	27	37 + 47 = 84	19	4-40
Geyskes[13]	1983	65	100	47 + 47 = 95	21	9 + 43 = 52	44	12-48
Tegtmeyer[14]	1984	109	94	37 + 63 = 100	27	23 + 71 = 94	65	0-60
Miller[15]	1985	65	87	85 + 15 = 100	15	15 + 44 = 59	34	> 6
Kuhlman[16]	1985	65	92	50 + 32 = 82	25	29 + 48 = 77	35	0-60
Martin[17]	1985	100	88	25 + 60 = 85	20	15 + 50 = 65	60	?
Grimm[18]	1986	53	100	58 + 35 = 93	26	4 + 26 = 31	27	1-60
Simonetti[19]	1987	110	83	60 + 26 = 86	25	37 + 45 = 82	67	48
Beck[20]	1987	33	88	71 + 28 = 100	7	4 + 59 = 73	22	1-60

Geyskes reports that in 10-15% of stenotic lesions, the PTA procedure cannot be performed because of technical limitations (failure to maneuver the balloon into the stenotic segment, complete occlusion, etc). In another 5% of patients, bleeding, thrombosis, or puncture of an artery interrupts the procedure prior to angioplasty. "Good" results were < 30% residual stenosis, "reasonable" results were 30-60% residual stenosis,and "deterioration" or "no result" criteria were also used. In 190 procedures, a good result was obtained in 76%, reasonable in 7%, no result in 14%, and deterioration in 3%.

Several factors influence the technical success of the PTA procedures and are listed in Table 16.

Table 16: Negative Influences on the Technical Success of PTA

1. Occlusion of the renal artery
2. Long stenotic segments ($\geq$ 10mm)
3. Renal artery at a sharp angle to the aorta
4. Atheromatous disease as etiology of stenosis (vs Fibromuscular disease)
5. Balloon size less than 90% of the artery diameter
6. Ostial lesions

Complications occurred in 71 (15 major, 56 minor) of 265 PTA procedures, and these are detailed in Table 17.

Table 17: Complications of PTA

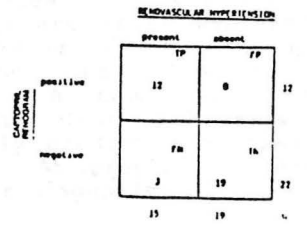
Complication	No	Sequel
Major complications (15 = 6%)		
Cholesterol emboli	3	One colonic bleeding one foot amputation
Anuric (one kidney)	2	Both recovered after bypass surgery
Arterial occlusion	1	Bypass surgery
Arterial bleeding*	2	Nephrectomy
Balloon rupture	1	Removed from femoral artery by surgery
Aneurysm puncture site	3	Corrected by surgery
Myocardial infarction	1	Died 1 mo later
Cerebrovascular accident (CVA)	1	Spontaneous uneventful recovery
Abdominal angina	1	Mesenteric bypass surgery
Minor complications (56 = 21%)		
Large groin hematoma	5	Spontaneous recovery
Spasm of (segmental) artery	33	Ten residual renal infarcts
subintimal placement of introduction of catheters or guide wires	18	Seven residual renal infarcts

*One of these patients was suspected for bleeding but at operation demonstrated a hyperperfused kidney [1]

Several other groups report salutory effects of PTA on blood pressure when PTA was performed to control BP (45-49). Follow-up in these studies is typically between 20 and 30 months, and report improvement in renal function and some increase (albeit swall, usually about 1 cm in length) in kidney size.

One other aspect of the treatment of the occluded renal artery should be noted, although the focus of this discussion has been on improvement in renal function. Geyskes et al (50) have evaluated the diagnostic/predictive importance of DTPA and I-hippurate scintography in 34 patients with unilateral renal artery stenosis. Criteria for a positive test in response to captopril 25 mg p.o. were: (1) the percentage uptake in the second minute by the affected/affected + contralateral kidney; (2) the time to peak of the affected minus the contralateral kidney; and, (3) the relative activity of hippurate at 15 minutes (vs 2 minutes). Using these criteria and defining a "positive" test as 2 of 3 of these criteria as "positive, 12 of 15 unilateral RAS patients had improved blood pressure after angioplasty. However, 6 patients with unilateral RAS without "positive" scintography had no improvement in blood pressure after angioplasty, and 13 patients with essential hypertension had no change in their scans with these criteria and captopril. Thus, as shown in Figure 18, the sensitivity of the captopril-DTPA-Hip maneuver was 80%, but the specificity for blood pressure improvement was 100%.

Figure 18: Value of Scintography as Predictor of BP Response



Operating characteristics of captopril renography in patients with and without renovascular hypertension. Sensitivity is 80% (12/15); specificity is 100% (19/19). TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

The most consistant change in the I-hippurate scan in this study was normal I-hippurate uptake, but a delay in I-hippurate excretion after captopril in stenotic kidneys. DTPA uptake was reduced in affected kidneys. These data are in agreement with a reduced GFR after captopril during preservation of RBF; hence, a marked decline in the filtration fraction occurred. The utility of this non-invasive tool in screening for predictability of operative or angioplastic result on blood pressure will be determined by future, prospective large trials.

V. Summary/Recommendations

Increased surveillance for patients with significant renal artery stenosis (either bilaterally or unilaterally in a solitary functioning kidney) is indicated because of the potential for improvement in function. Clues to the presence of the disease are hypertension (recent onset, difficult to control, or a change in pattern), deterioration in function with good BP control, and evidence of wide spread atherosclerosis (history of TIA's, claudication, angina, and a smoker). The workup of the patient should include renal sonography (to eliminate a disparity in kidney size or an aneurysm), a T^{C}-DTPA scan +/- captopril (if the patient is an operative or PTA candidate), and arteriography (if a candidate for a reparative procedure). Treatment, aside from good BP control, would include PTA for amenable lesions or a renal artery bypass (aortorenal, splenorenal, or hepatorenal.

It is clear from a review of this subject that the diagnostic and therapeutic options are still evolving in occlusive renal vascular disease. The role of scintography in unilateral disease is hopeful, but its value in bilateral disease is insufficiently known. A combination of Tc-DTPA (for GFR measurement) and I-Hip (for RBF measurement) may enable physicians to accurately predict the presence of stenosis non-invasively in future. At present, arteriography remains the definitive procedure for diagnosis.

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