RENOVASCULAR HYPERTENSION

Internal Medicine Grand Rounds

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Index to Contents

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I. INTRODUCTION

In the large population of patients with established hypertension, there exists a subgroup in whom the blood pressure elevation is secondary to renal ischemia. These patients have renovascular hypertension which is the most prevalent form of curable hypertension. Nevertheless, continuing controversy surrounds the screening procedures and work-up of patients with renovascular hypertension. The identification of patients with renovascular hypertension has been so complex and imprecise that the diagnostic quest has been challenged (McNeil et al, 1975; McNeil and Adelstein, 1975). However, it has also become apparent that renovascular hypertension is a progressive disease with serious sequelae if appropriate therapy is not rendered (Dean et al, 1981; Hunt and Strong, 1973). Hence the challenge remains, despite controversy, to identify those patients in whom the preferred therapy is relief of renal ischemia.

In the evaluation of patients with renovascular hypertension, differences of opinion can be anticipated on several grounds. First and foremost, renovascular hypertension is a retrospective diagnosis. The renal arteriogram may reveal renal artery stenosis but its relationship to hypertension is established only by improvement in or cure of hypertension following surgery or balloon angioplasty of the offending lesion. Other tests such as intravenous pyelogram (IVP), radionuclide studies, peripheral and renal vein renins are non-specific and may yield false positive or false negative results.

Second, renovascular hypertension is an "uncommon" disorder. Based on the referral pattern, estimates of prevalence range from 0.2 to 10% of the hypertensive population. Such a low prevalence compared to primary hypertension does not attract aggressive diagnostic work-up. Since renovascular hypertension is relatively uncommon, even a reliable screening test will result in subjecting large number of patients with essential hypertension to unnecessary procedures. While there may be certain clinical clues, they are not sufficiently strong enough to discriminate renovascular from essential hypertension.

Third, with modern antihypertensive drugs (angiotensin converting enzyme [ACE] inhibitors, beta-blockers, calcium antagonists), renovascular hypertension can be treated medically. There is emerging evidence, however, that the long-term outlook for patients with renal artery stenosis who are treated medically is less favorable to surgical treatment despite attainment of satisfactory control of hypertension.

The prevalence of renovascular hypertension, the need for accurate diagnosis, and the comparative value of different therapeutic modalities remain poorly defined. In some centers, a systematic search is made to uncover renovascular hypertension. Other centers seldom evaluate patients for renal artery stenosis. There are several reasons for this disparity

in clinical evaluation and diagnostic approach - emphasis on the infrequency of secondary hypertension, variable cure rate of hypertension by the operative treatment, high cost of diagnostic tests, and improvements in drug therapy. Unfortunately, conflicting results of such studies have engendered a lack of uniformity in the approach to patients with suspected renovascular hypertension. In this Grand Rounds, diagnostic studies and therapeutic options for renovascular hypertension will be reviewed with emphasis on their current status and value.

Table 1: Incidence of Renal Arterial Lesions in Normotensive and Hypertensive Patients. (Data from Eyler WR, et al: Radiology 1962;78:879.

Age	Normotensive		Hypertensive	
	Normal	Lesion	Normal	Lesion
31-40	7	3	6	10
41-50	26	8	14	22
51-60	99	35	28	50
Over 60	69	56	15	48

II. DEFINITION: Renal Arterial Disease versus Renovascular Hypertension

Renovascular hypertension refers to hypertension resulting from renal ischemia - whereas in renal arterial disease, the occlusive lesion may or may not be sufficient enough to increase the systemic blood pressure. Why is this distinction important? In renovascular hypertension, reperfusion of the kidney is expected to cure or improve the blood pressure. In renal arterial disease, surgery or balloon angioplasty may not necessarily ameliorate the course of hypertension. The effects of renal artery stenosis and its relief on renal function is a different matter which will be discussed elsewhere in this Grand Rounds. With the development of angiography, it has become apparent that renal artery stenosis can be seen in normotensive individuals (Eyler et al, 1962 (Table 1). Autopsy studies have further substantiated the coincidental occurrence of renal artery stenosis in non-hypertensive patients (Holley et al, 1964). Thus, the mere presence of renal artery stenosis in a hypertensive patient does not establish a causal connection between the two entities. The value of establishing a link between hypertension and renovascular disease was emphasized by Homer Smith several years ago (Smith, 1956) who estimated that only 19% of patients subjected to unilateral nephrectomy experienced amelioration of their hypertension. He realized this as a false interpretation of Goldblatt's experimental hypertension produced by clamping the renal artery of dogs. Fortunately, recent advances in our understanding of the experimental renal hypertension and of the spectrum of renovascular disease have improved our ability to identify and treat patients with renovascular hypertension.

III. HISTORICAL ASPECTS

The history of renovascular hypertension can be traced to Richard Bright who in 1827 demonstrated an association between "hardness" of the pulse, proteinuria, and dropsy with "hardening" of the kidneys (Bright, 1827). His astute observations implicated a pivotal link between the renal disease and disturbances of circulation. That this disturbance was hypertension was suspected by Traube in 1856 (Traube, 1856). Finally, Mahomed in 1874 (Mahomed, 1874) reported "high tension" in the arterial system of patients suffering from renal disease. Although Bright did not draw a causal relationship between hypertension and cardiac enlargement, he made the remarkable observation that "the altered quality of blood so affects the minute and capillary circulation as to render greater action necessary to force the blood through the distal division of the vascular system." Encouraged by Bright's observations, several investigators embarked on a path to recreate the findings in experimental models. Growitz and Israel in 1879 produced acute occlusion of one renal artery or performed unilateral nephrectomy to decrease the renal mass (Growitz and Israel, 1879). Earlier investigators may have preempted Goldblatt's observations had their experiments included blood pressure measurements. In 1880, Lewinski produced cardiac hypertrophy in dogs after partial constriction of renal arteries (Lewinski, 1880). In 1905, Katzenstein reported blood pressure elevation in dogs with experimental renal occlusion (Katzenstein, 1905). More critical than the dependence of hypertension on reduced renal perfusion was the observation that the elevated pressures returned to normal when the constricting bands were removed. Katzenstein's notable studies preceded Goldblatt's experiments by nearly 30 years but ironically as it turned out he erroneously believed that since the duration of renal artery occlusion was so short that the blood pressure could not be of renal origin. A landmark in our knowledge of renovascular hypertension was Tigerstedt and Bergman's description in 1898 of renal pressor substance in the rabbit (Tigerstedt and Bergman, 1898). They called this crude substance "renin" which has since become an important regulator of cardiovascular homeostasis. Although their work took place in 1911 (Senator, 1911), it was left to Goldblatt to confirm the nature of renovascular hypertension (Goldblatt, 1934).

The demonstration by Goldblatt and co-workers that constriction of the renal artery in dogs caused hypertension heralded a new era in the understanding of hypertensive mechanisms (Figure 1). Working as a pathologist, Goldblatt noticed that extensive vascular abnormalities were present at autopsy of patients with hypertension. About 40 years later reflecting on his own work, he stated: "Contrary, therefore, to what I had been taught, I began to suspect that vascular disease comes first and, when it involves the kidneys, the resultant impairment of the renal circulation probably, in some way, causes elevation of blood pressure" (Goldblatt, 1977). Although renal revascularization procedures were not done at that time, Goldblatt's observations proved that hypertension secondary to renal ischemia could be corrected by nephrectomy. He was convinced that his canine models were paradigms of human renovascular hypertension. The past several years have witnessed a mounting vindication of Goldblatt's concepts about renin and hypertension.

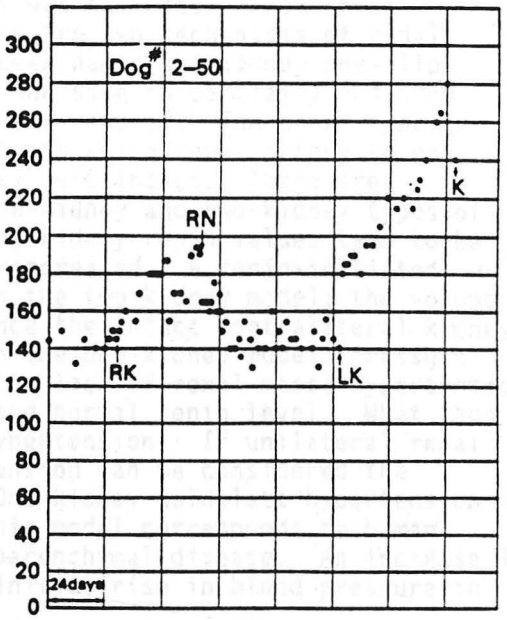


Figure 1: Graph of mean blood pressure recording of dog in Goldblatt's experiment. RK, right main renal artery moderately constricted. RN, right nephrectomy. LK, severe constriction of left main renal artery. K, animal sacrificed. Reproduced with permission from Goldblatt: Ann Intern Med 1937;11:69.

The first documented case of human renovascular hypertension was reported in 1938 (Ledbeter and Burkland, 1958); hypertension in a 5 year old child was cured by the removal of an ischemic right kidney. The first cure of hypertension by renal revascularization was reported by Freeman in 1954 who performed bilateral renal artery thromboendarterectomy (Freeman, 1954). During the late 1950s, in many centers, aortography became available permitting identification of renal artery stenosis. By 1960, however, it became apparent that renal artery stenosis revascularization did not always result in the reduction of blood pressure in hypertensive individuals. With the refinements in biochemical and radiologic techniques in the last two decades, interest in renovascular hypertension has again been rekindled and sustained.

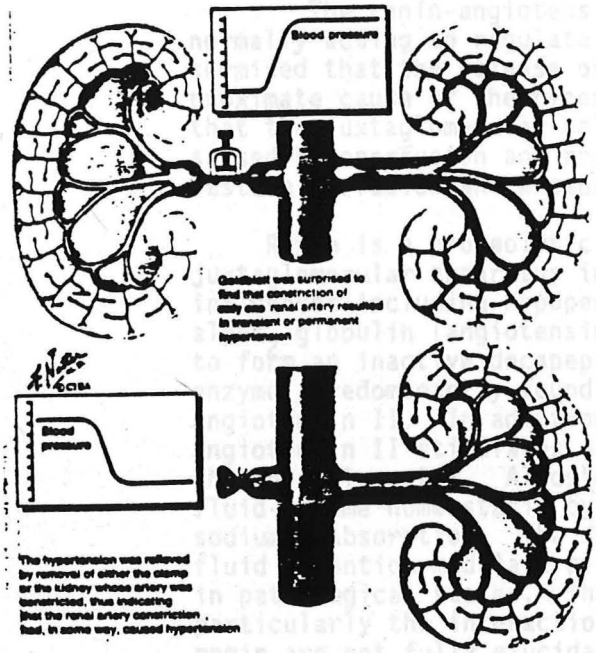
The concept of renovascular hypertension had its beginning in the nineteenth century. Physiologic and biochemical explanations were offered in the 1930s. Then there was a period of lull for a quarter century. The 1950s saw the advent of aortography and in the 1960s problems related to the diagnosis of renovascular hypertension were addressed. The pressor function of the ischemic kidney was further elucidated in the 1960s and 1970s by Laragh and many other workers. In the present decade, we have witnessed the utilization of newer techniques - digital subtraction angiography and percutaneous balloon angioplasty. Of course, surgical revascularization techniques have been refined and rendered safe in experienced hands. From the days of Richard Bright, much progress has been made in the mechanisms and management of renovascular hypertension.

IV. THE BASIS OF EXPERIMENTAL RENOVASCULAR HYPERTENSION

In Goldblatt's experiments, constriction of one renal artery caused moderate hypertension whereas severe hypertension resulted when one kidney

was removed and the other renal artery was occluded. From these observations, it was evident that there are two mechanisms of renal ischemic hypertension. One type has been named one-kidney one-clip hypertension in which renal artery on one side is partially occluded (clipped) and the contralateral kidney is removed. The other type is called two-kidney one-clip hypertension in which renal artery to one kidney is occluded, the other kidney is left intact. There are interesting differences between the one-kidney and two-kidney types of hypertension; in the former, plasma and kidney renin values tend to be normal whereas in the latter they are increased. A renin-initiated vasoconstrictor state is implicated in the two-kidney model; the volume component is not a major mechanism since the intact contralateral kidney responds by promoting natriuresis. In the one-kidney model, pressure induced natriuresis is absent due to the lack of renal mass; hypertension is characterized by volume expansion and normal renin level. What then is the corollary to human renovascular hypertension. If unilateral renal artery stenosis is present the hypertension can be considered the equivalent of the two-kidney model. One-kidney Goldblatt hypertension is characterized by sodium retention. This model corresponds to human renovascular hypertension plus renal parenchymal disease. An increase in renin release is responsible for the initial rise in blood pressure in both models.

Figure 2: Renovascular hypertension and the Goldblatt experiment. Copyright 1973 CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reproduced, with permission, from Clinical Symposia, illustrated by Frank H. Netter, M.D. All rights reserved.)



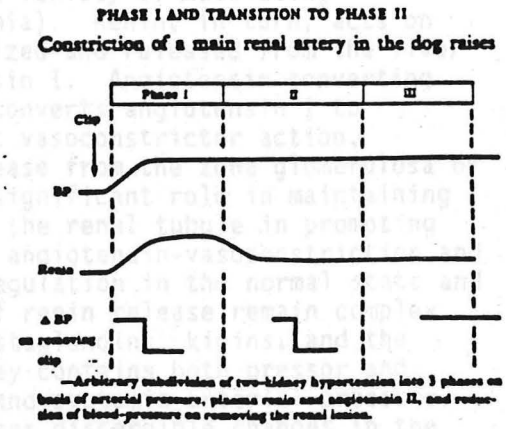


Figure 3: (Data from Brown et al, Lancet 1976;1:1219-21).

The course of experimental two-kidney, one-clip hypertension has been studied by Brown and colleagues (Brown et al, 1976) (Figure 3). Initially, both the renin output and the blood pressure increase. In the following phase, a high blood pressure level is maintained but the renin level falls. Despite this sequence, the renin dependence of hypertension can be unmasked by the fall in blood pressure when angiotensin inhibitors are administered (Wallace and Morton, 1984; Brunner et al, 1971). Up to now, removal of the clip results in a fall in the blood pressure. In the next and chronic phase, the blood pressure remains elevated even after the removal of the clip reflecting vascular damage in the other kidney. This last observation may explain why correction of renal artery stenosis does not resolve hypertension in some individuals.

A. RENOPRIVAL FACTORS

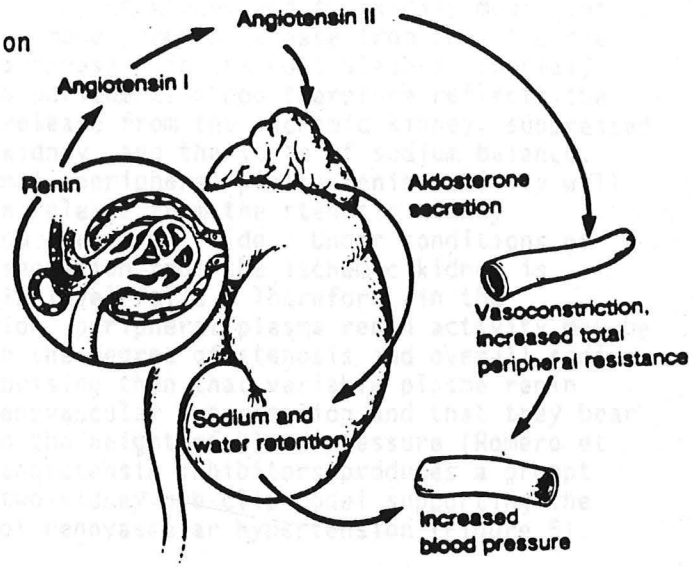
Although it was believed that hypertension could not be sustained after bilateral nephrectomy (Goldblatt, 1937), Dr. Grollman subsequently showed the occurrence of hypertension in the anephric state (Grollman et al, 1949). While some workers believed that hypertension was a consequence of volume excess, others attributed it to the elimination of renal vasodepressor mechanisms. Implantation of the kidney interstitial cells blunts the development of renoprival hypertension in rabbits (Muirhead et al, 1972). While it has been extremely difficult to prove, deprivation of renal vasodepressor substances may contribute to the hypertension in renovascular or renal parenchymal dysfunction.

B. RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The renin-angiotensin system is a physiological feedback mechanism normally acting to regulate circulatory and volume homeostasis. Goldblatt surmised that the release of a pressor enzyme, renin, was the most proximate cause of the hypertension in his experiments. He pointed out that the juxtaglomerular cells, being distal to the renal artery stenosis, sensed hypoperfusion and reactively secreted renin at an increased rate to restore perfusion which caused hypertension in the arterial circulation.

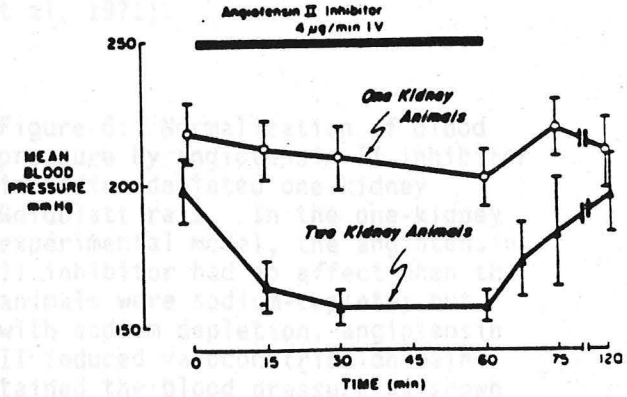
Renin is a proteolytic enzyme that is liberated from the juxtaglomerular apparatus in response to a variety of modulating influences including hypoperfusion (ischemia). Renin, in turn, acts on alpha$_2$-globulin (angiotensinogen) synthesized and released from the liver to form an inactive decapeptide, angiotensin I. Angiotensin converting enzyme (predominantly found in the lung) converts angiotensin I to angiotensin II. In addition to its potent vasoconstrictor action, angiotensin II stimulates aldosterone release from the zona glomerulosa of the adrenal cortex. Aldosterone plays a significant role in maintaining fluid-volume homeostasis by its action on the renal tubule in promoting sodium reabsorption. The dual effects of angiotensin-vasoconstriction and fluid retention-modulate blood pressure regulation in the normal state and in pathological states. The mechanisms of renin release remain complex particularly the interactions between prostaglandins, kinins, and the renin are not fully elucidated. The kidney contains both pressor and depressor hormones that control regional and systemic arterial pressure. Any dysregulation of these mechanisms causes discernible changes in the systemic blood pressure.

Figure 4: Angiotensin conversion



While the pathophysiology of renin secretion has been elegantly elucidated, the precise role of vasodepressor substances has remained elusive. If a depressor renal hormone does exist, many paradoxes of renovascular hypertension can be explained. For example, the occasional absence of increased renin content from ischemic kidneys, fall in blood pressure following surgical correction of renal artery stenosis despite a low or normal renin level. Due to multiple and competing stimuli, the level of plasma renin activity is a function not only of the afferent arteriolar pressure but also of sodium efflux in the macula densa region.

Figure 5: Blood pressure changes in renal hypertension induced by angiotensin II inhibitor. Infusion of an angiotensin II inhibitor produced an immediate fall in blood pressure in the two-kidney form of experimental renovascular hypertens ion exposing the renin factor. In contrast, the inhibitor caused no change in the sodium expanded one-kidney model. (From Brunner HR, et al, Science 1971;174:1344-46).



With these variable influences on the renin-angiotensin system, let us examine the role of renin in the one-kidney and two-kidney models of hypertension. In the two-kidney model, renin release from the ischemic kidney is activated and it is suppressed in the contralateral (normal) kidney. The renin level in the peripheral blood therefore reflects the net effect of augmented renin release from the ischemic kidney, suppressed renin release from the normal kidney, and the state of sodium balance. When the sodium balance is normal, peripheral plasma renin activity will be elevated only when the renin release from the stenotic kidney supersedes the renin output from the normal side. Under conditions of positive sodium balance renin secretion from the ischemic kidney is reduced and the peripheral renin level falls. Therefore, in the two-kidney, one-clip hypertension, peripheral plasma renin activity may be elevated or normal depending on the degree of stenosis and overall sodium balance. It should not be surprising then that variable plasma renin levels have been reported in renovascular hypertension and that they bear no quantitative relationship to the height of blood pressure (Romero et al, 1977). Administration of angiotensin inhibitors produces a prompt fall in blood pressure in the two-kidney one-clip model supporting the renin dependency in this form of renovascular hypertension (Figure 5).

In the one-kidney hypertension, peripheral renin activity goes up initially but quickly falls to a low level presumably as a result of the inability of the single occluded kidney to excrete sodium and water (Tobian et al, 1964). In this type, hypertension is not renin dependent unless sodium depletion occurs (Gavaras et al, 1973) (Figure 6). It should be emphasized that in the one-kidney model, sodium depletion alone does not normalize the blood pressure but renders the hypertension sensitive to renin-angiotensin inhibitors. It can be concluded that the one-kidney model with salt overload exhibits low-renin, volume dependent hypertension that can be converted into renin dependent hypertension by salt depletion, or the blood pressure elevation in the one kidney hypertension is indeed sustained by renin-angiotensin system that is resistant to blocking agents. Even the explanation for two-kidney hypertension is not a simple one. As hypertension persists, the renin levels falls invoking a volume mechanism to elevate venous pressure and peripheral vascular resistance (Pals et al, 1971).

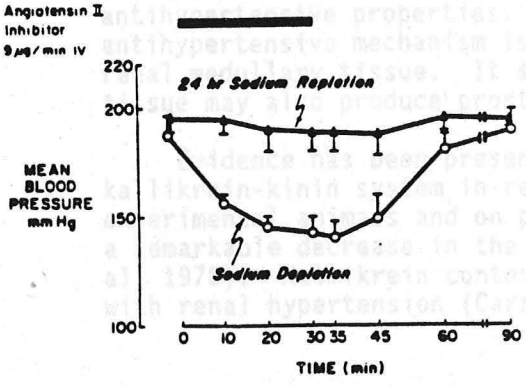


Figure 6: Normalization of blood pressure by angiotensin II inhibitor in sodium depleted one-kidney Goldblatt rats. In the one-kidney experimental model, the angiotensin II inhibitor had no effect when the animals were sodium-replete; but with sodium depletion, angiotensin II induced vasoconstriction maintained the blood pressure as shown by the dramatic fall in blood pressure induced by the inhibitor during sodium depletion. (From Gavras H et al, Science 1973;180:1369-72).

C. OTHER POSSIBLE PRESSOR MECHANISMS

Besides the overwhelming role of the renin-angiotensin system, other pressor or depressor mechanisms have been invoked in the genesis of chronic renovascular hypertension (Davis, 1977; McPhaul et al, 1966). Evidence has been presented that a renal pressor substance other than renin is responsible for renovascular hypertension. Grollman and Krishnamurthy from this institution coined the term "nephrotensin" for the newly discovered pressor agent (Grollman and Krishnamurthy, 1971, 1973). Subsequent work, however, revealed that the putative substance was angiotensin I bound to alpha$_2$-globulin (Schweikert et al, 1972). This observation settled the nature of the Grollman factor until the issue was reopened by careful application of angiotensin II blockade (Susic and Sparks, 1975). It was noted that the pressor actions of nephrotensin were not altered by angiotensin blockade. Skeggs and co-workers reinvestigated the possibility of non-renin factors in renal hypertension and reported a lowering of arterial pressure in response to immunization with a protein from the non-renin fraction of kidney extracts (Skeggs et al, 1975, 1976). These experiments suggest that a non-renin pressor substance may be responsible for one-kidney hypertension in rabbits.

Many lines of evidence suggest that renal anti-hypertensive mechanisms may be involved in the pathogenesis of renovascular hypertension (Davis, 1977). Several substances - prostaglandins A and E, renal kinins, neutral renomedullary lipid (of Muirhead) - have been considered as possible candidates mediating the vasodepressor function of the kidney. Both PGA and PGE lower the blood pressure by their systemic or renal actions. Furthermore, prostaglandins may affect renin release and modulate renal blood flow, tubular sodium reabsorption, and sodium concentration in the renal medulla (Tobian et al, 1976; Anderson et al, 1976). Whereas the renal origin of PGE$_2$ is well established, uncertainty surrounds the formation of PGA. This is an important consideration since PGA is not destroyed in its passage through lungs and can conceivably exert systemic vasoactive actions. Some workers have reported low levels of PGA in patients with essential hypertension (Zusman et al, 1973; Lee and Attallah, 1975). Muirhead's discovery of renomedullary lipid marked another intriguing development in the field of renal hypertension (Muirhead et al, 1975). It was revealed that auto- or isotransplantation of renomedullary tissue lowered arterial pressure in experimental renal hypertension. The arterial pressure went up after the removal of the transplanted material and dead renomedullary extract had no effect on the blood pressure. Thus, renal medullary cells appear to exert non-excretory antihypertensive properties. Muirhead has proposed that the antihypertensive mechanism is mediated by neutral lipid elaborated by the renal medullary tissue. It should be remembered, however, that the same tissue may also produce prostaglandins.

Evidence has been presented concerning the role of the kallikrein-kinin system in renal hypertension. Observations on experimental animals and on patients with renovascular hypertension showed a remarkable decrease in the urinary excretion of kallikrein (Keiser et al, 1976). Kallikrein content of the kidney tissue is decreased in rats with renal hypertension (Carretero et al, 1974). These data indicate that

kinins, perhaps bradykinin might have a role in renal hypertension. While an aberration in prostaglandin and kallikrein systems may initiate or maintain renal hypertension, the data are not conclusive.

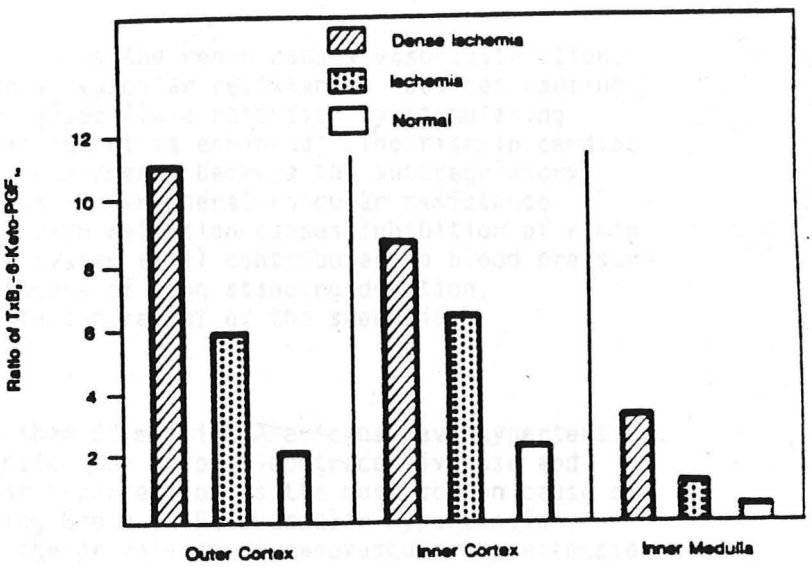


Figure 7: Ratio of TxB_2-6-keto-PGF_{1a} production by different regions of kidney. TxB_2 indicates thromboxane B_2; PGF_{1a}, prostaglandin F_{1a}. (From Anderson et al, JAMA 1984;251:3118-20).

Excessive thromboxane production has been reported in a patient with renal artery stenosis (Anderson et al, 1984) (Figure 7). Unlike PGE_2, which is a vasodilator, thromboxane is a potent vasoconstrictor substance. Measurement of prostanoid generation by cortical and medullary tissue of a patient with renal artery stenosis revealed thromboxane production by the ischemic zone. Since a systemic action of renal thromboxane is unlikely, its local effects can cause vasospasm and platelet aggregation thereby increasing renin production. It has been demonstrated that selective inhibition of thromboxane synthesis attenuates the development of one-kidney Goldblatt hypertension (Sutter and Weeks, 1982). These findings underscore the complexity of non-renin mechanisms involved in the pathogenesis of renovascular hypertension.

To summarize, several hemodynamic and hormonal changes occur in renovascular hypertension. As discussed, these patterns change with the evolution and establishment of permanent hypertension. The following sequence best explains the factors involved in initiation and maintenance of human renovascular hypertension. When the stenosis reaches a critical magnitude, the resultant hypoperfusion to the juxtaglomerular apparatus stimulates the renin release. Since the early observations of Mann (Mann et al, 1938), the concept of "critical stenosis" has been generally accepted (Young et al, 1977). While most observations relate to peripheral blood vessels, certain principles can be applied to renal artery stenosis. Arteriographic demonstration of renal artery stenosis, although important, does not correlate with systemic hemodynamics. It has

been proposed that a reduction of renal arterial lumen of about 60% of the diameter or 84% of the cross sectional area is necessary to produce significant hemodynamic effects (Haimovici and Zinicola, 1962). However, this may not apply to bilateral renal artery stenosis or stenosis of a solitary kidney.

The angiotensin II generated by the renin causes vasoconstriction, thereby increasing the peripheral vascular resistance. Besides causing vasoconstriction, angiotensin causes fluid retention by stimulating aldosterone secretion. Cardiac output is enhanced. The rise in cardiac output tends to be a temporary phenomenon because the autoregulatory response leads to a further rise in peripheral vascular resistance (Meininger, 1985). Although sodium retention causes inhibition of renin release, the renin-angiotensin system still contributes to blood pressure elevation. In renovascular disease of long standing duration, hypertension may persist despite the relief of the stenosis.

V. PREVALENCE

It is estimated that more than 60 million Americans have hypertension. With the exception of hypertension due to oral contraceptive use and alcohol ingestion, renovascular hypertension is the most common cause of remediable hypertension (Working Group on Renovascular Hypertension, 1987). The available data on the prevalence of renovascular hypertension have been generated from centers with special interest in hypertensive disorders. Consequently the true incidence of renovascular hypertension remains unknown. At some institutions, renovascular hypertension is frequently diagnosed, whereas at others, it remains a curiosity. Because many centers search for the presence of renovascular hypertension only when blood pressure is poorly controlled, the reported incidence is highly variable. In interpreting the published reports of incidence, keep in mind that the numbers were obtained when the diagnostic criteria were too rigid and the screening procedures were less sensitive. Furthermore, a negative screening procedure at some point during the patient's clinical course does not exclude the future occurrence of renal artery stenosis, particularly the atherosclerotic type. Thus I would view the published figures with some caution. Keeping this in mind, let us examine the incidence of renovascular hypertension:

- Available data indicate that less than 0.5% of the hypertensive population has renovascular hypertension (Working Group on Renovascular Hypertension, 1987). I suspect that the figure is close to or greater than 1-2%.

- In referral centers, 2 to 4% have renovascular hypertension (Ferguson, 1975; Gifford, 1969).

- In unselected patients, it is probably less than 1% (Danielson and Dammstroom, 1981; Rudnick et al, 1977; Berglund et al, 1976; Balding et al, 1967).

- The prevalence is significantly higher in patients with accelerated and malignant forms of hypertension. For example, 7% of the blacks

and 32% of whites with Grades III or IV hypertensive retinopathy had renovascular hypertension (Davis et al, 1979). Also, in those with severe hypertension and azotemia, there is a higher incidence of renovascular hypertension (Ying et al, 1984).

- In the surgical literature, the purported incidence of renovascular hypertension is high ranging from 5% to 10% of the hypertensive population (Dean, 1985), reflecting the special population group with difficult hypertension.

- The Mayo Clinic experience revealed relative rarity of renovascular hypertension (Tucker and LaBarthe, 1977). It was reported that only 0.18% of their hypertensive population underwent an operation for renovascular hypertension. This figure can be questioned on the grounds that not all the screened patients underwent arteriography and repeat visits by patients with essential hypertension were not enumerated.

- The incidence of renovascular hypertension in some referral centers tells a different story; Foster and colleagues diagnosed renovascular hypertension in 145 of 403 consecutive patients (36%) (Foster et al, 1969). Similarly, Poutasse observed renal artery stenosis in 173 of 617 patients (28%) undergoing arteriography (Poutasse, 1961). In the same year, Perloff and colleagues reported renal artery stenosis in 70 of 109 patients (64%) (Perloff et al, 1961). Since correction of renal artery stenosis did not influence the blood pressure in some patients, the prevalent figure was actually 13%, still a high number. Shapiro and co-workers found renal artery stenosis in 115 of 212 hypertensive patients (54%) (Shapiro et al, 1969). Follow-up evaluation revealed only 6% had true renovascular hypertension judged by blood pressure response.
- Capelli and co-workers evaluated 104 consecutive patients for renovascular hypertension (Capelli et al, 1973) and noted a 6% prevalence.

- During a 5 year period, Ayers and colleagues at the University of Virginia Hospital diagnosed renal artery stenosis in 10% of 185 patients (Ayers et al, 1973) but true renovascular hypertension judged by blood pressure response to surgery was noted in a smaller number.

- Amongst 750 patients with severe hypertension, a 5-7% incidence of renal artery stenosis was noted in one report (Kennedy et al, 1965).

- In the large National Co-operative Study on Renovascular Hypertension, involving 2,442 patients, the incidences of renovascular disease and renovascular hypertension were 36% and 20%, respectively (Maxwell et al, 1972). The data derived were such that a true prevalence could not be estimated. This is truly unfortunate because this is one of the best studies to date to distinguish renovascular disease from renovascular hypertension.

The purpose of any epidemiologic study is to help the clinician to select appropriate patients for further testing in a cost effective fashion. If the epidemiologic analysis revealed that a particular narrow proportion of hypertensive patients should be targeted for renovascular hypertension, the decision making process is straight forward. Unfortunately, survey of the literature provides no such information. The data summarized above were obtained when renal arteriography was uncommonly performed and the interpretation of screening tests (IVP, scintiscan) was not standardized. All the studies suffer from the recurring errors of retrospective analysis - poor or no follow-up, incomplete data collection and improper interpretation, and heterogeneity of clinical definitions.

While one can argue that only a small percentage of hypertensives have renovascular hypertension, the absolute number is by no means small. Even if we assume a low prevalence rate, close to or in excess of 1 million Americans harbor potentially correctable renovascular hypertension.

Table 2: PATHOLOGY

1. Atherosclerosis
2. Fibrous and fibromuscular lesions--sub-classified into intimal, medial, peri-medial and adventitial dysplasias
3. Arteritis
4. Aneurysms/Dissections
5. Thrombosis-Embolism

VI. PATHOLOGY OF RENAL ARTERY STENOSIS

Although a variety of pathological lesions may cause renovascular hypertension, the basic lesion is stenosis of the renal artery caused by atherosclerosis or fibromuscular dysplasia, the two most common causes.

A. ATHEROSCLEROTIC LESIONS

The atherosclerotic lesion accounts for about two-thirds of the cases and may be localized to the renal artery but more often occurs as a component of generalized atherosclerosis (Ernst et al, 1973). The lesion tends to be orificial or occurs in the proximal third of the artery and is bilateral in about one-third of cases (Foster et al, 1975). Pathologically, there is nothing special about atherosclerosis of the renal artery. The pathogenesis and pathology parallel that of atherosclerosis elsewhere with considerable intimal thickening and cholesterol laden lipid deposition. The lesion consists of intimal fibrous plaques, generally eccentrically located producing an irregular luminal surface. It should be appreciated that the presence of atherosclerotic disease in the renal artery is not synonymous with renovascular hypertension. Essential hypertension may indeed antedate or co-exist with renal artery stenosis. In one series, nearly 50% of

patients with atherosclerotic renal artery stenosis at autopsy had no history of hypertension (Holley et al, 1964). Thus, the lesion appears to be common. Males are affected twice as often as females. These sex differences disappear with advancing age. The prevalence of renovascular atherosclerosis is age-dependent (Schwart and White, 1964).

Nearly half of the individuals with significant renal artery stenosis on one side have evidence of contralateral renovascular disease. Right and left sided renal arterial lesions occur with equal frequency although for some reason the stenosis on the left side tend to be severe. The propensity for plaque to occur in the ostia and proximal portions of the artery is in keeping with the genesis of atherosclerotic lesions elsewhere. Increased velocity of blood flow and turbulence cause endothelial injury, platelet deposition, and migration of medial smooth muscle to intimal regions - predisposing to plaque formation. Renal atherosclerosis progresses in the same way as atherosclerosis elsewhere. Often, there is arteriographic evidence of asymptomatic abdominal aortic atherosclerosis. Occasionally renal artery stenosis is the only manifestation of atherosclerosis.

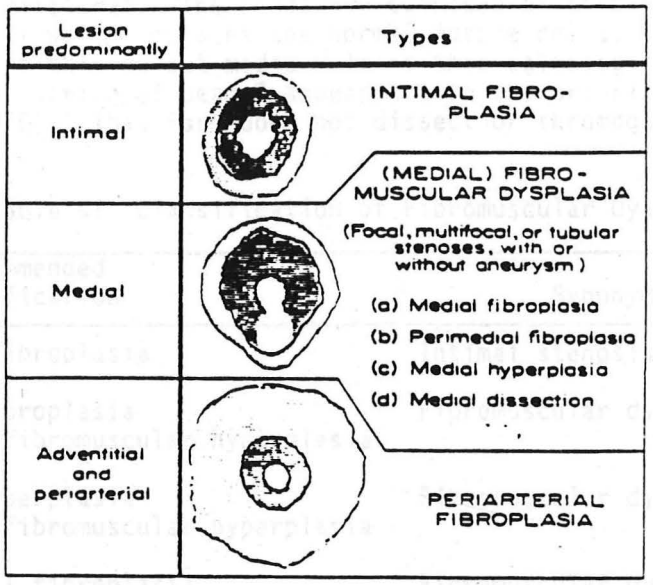
B. FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia of the renal arteries is the most common cause of renovascular hypertension in persons under 40 years of age, although it has been reported from infancy to ripe old age (Hunt et al, 1973). Categorized under a single term, these lesions represent an assortment of histological patterns. They are subcategorized according to the morphological appearance and the layer of arterial wall involved (Harrison et al, 1971) (Table 3) (Figure 8).

Table 3: Features of Atherosclerotic and Fibrous Renal Artery Disease

Renal Artery Disease	Incidence (%)	Age (yr)	Location of Lesion in Renal Artery	Natural History
Atherosclerosis	60	>50	Proximal 2 cm; branch disease rare	Progression in 50%, often to total occlusion
Fibrous dysplasias:				
Intimal fibroplasia	4–5	Children, young adults	Mid-main renal artery and/or branches	Progression in most cases; dissection and/or thrombosis common
Medial fibroplasia	30	25–50	Distal main renal artery and/or branches	Progression in 33%; dissection and/or thrombosis rare
Periarterial fibroplasia	4–5	15–30	Mid-to-distal main renal artery or branches	Progression in most cases, dissection and/or thrombosis common
Fibromuscular hyperplasia	<1	Children, young adults	Mid-renal artery or branches	Progression in most cases

Figure 8: The Mayo Clinic classification of fibrodysplasia.



- INTIMAL DYSPLASIA. Intimal lesions are rare and occur in less than 5% of all cases with fibrodysplasia. Essentially detected in children, the lesion is short and smooth with concentric narrowing of the renal artery. The lesion consists of irregular subendothelial mesenchymal cells with normal medial and adventitial layers.

- MEDIAL HYPERPLASIA. This is the least common lesion accounting for less than 1% of all fibroplastic entities. Pathologically, the lesion is characterized by preserved yet excessive medial smooth muscle architecture. On the arteriogram it appears as an isolated mural concentric narrowing of the renal artery. It occurs predominantly in women in their third decade and is a rapidly progressive disorder.

- PERIMEDIAL (Subadventitial) FIBRODYSPLASIA. This lesion accounting for about 10% renal artery dysplasias occurs in women between the fourth and fifth decades. Grossly on the angiogram, the lesion resembles media dysplasia. Microscopically there is an accumulation of elastic tissue between the media and adventitia, the intima being normal.

- MEDIAL FIBRODYSPLASIA. This is the most common form of fibromuscular dysplasia and accounts for well over 85% of all dysplasia lesions. This lesion is noted predominantly in young women. The medial fibromuscular dysplasias are sub-divided into four types: medial fibroplasia, perimedial fibroplasia, medial hyperplasia, and medial dissection. Medial fibroplasia is also referred to as fibromuscular hyperplasia but this description is misleading, since there is no true muscular hyperplasia. It is

characterized by a series of circumferential fibrous rings generally affecting the distal two-thirds of the artery and is often bilateral. The rings are composed of thickened collagenous material which replaces the normal muscle cells, alternating with areas of thinned-out media. It is this pathological pattern that causes "string of beads" appearance on the arteriogram (Stewart et al, 1970). This form does not dissect or thrombose.

Table 4: Classification of Fibromuscular Dysplasia

Recommended Classification	Synonyms
Intimal fibroplasia	Intimal stenosis
Medial fibroplasia fibromuscular hyperplasia	Fibromuscular dysplasia;
Medial hyperplasia fibromuscular hyperplasia	Fibromuscular dysplasia;
Perimedial fibroplasia perimural fibrosis; medial fibroplasia; subadventitial fibroplasia; medial hyperplasia	Fibromuscular dysplasia;
Periarterial fibroplasia periarterial fibrous stenosis	Subadventitial fibroplasia;

The etiology of fibrous dysplasias is not fully understood. Many theories have been explored. The preponderance in women suggests hormonal influences but no proof is available (Stanley et al, 1975; Stanley and Graham, 1981). Similarly, the common association between ptotic kidneys and fibrodysplasias led to the proposal that arterial stretching may be a factor (Kaufman and Maxwell, 1963). Mural ischemia resulting from functional defects in vaso vasora supplying the renal arterial wall has been implicated (Sottiurai et al, 1978). At the present time there is no consensus about the pathogenesis of fibromuscular dysplasias.

VII. NATURAL HISTORY OF RENAL ARTERY STENOSIS

Although there have been few reports describing the natural history and course of renal arterial lesions, limited available data suggest the disease is progressive in patients with atherosclerotic disease (Wollenweber et al, 1968) as well in those with fibrodysplastic lesions (Meaney et al, 1968). There is a growing body of clinical evidence to indicate the progressive nature of atherosclerotic disease not only in the renal arteries but elsewhere in the body. The importance of progression has recently been addressed by the Cleveland group (Schreiber et al,

1984). These workers performed serial angiographic studies in 85 patients with atherosclerosis over a 52 month period and noted progressive vascular disease in 44% of the patients. In 14 patients total arterial obstruction occurred. Not unexpectedly, renal function declined in patients with progressive renal arterial disease. It is not possible to predict from angiography which lesions will progress and which will not.

Progression of renal artery fibromuscular dysplasia is now well documented (Lorelis et al, 1985; Goncharenko et al, 1984; McCormack et al, 1967). In one study, follow-up observations during an 11 year period identified progression of renal artery fibromuscular dysplasia in all the 42 patients (Goncharenko et al, 1981). In the Lorelis study, progression or bilateral occurrence of fibromuscular dysplasia was seen in 19 of 20 patients with a mean follow-up of 6 years. Anatomical progression did not correlate with clinical status of the patients. Despite the progressive nature of fibromuscular dysplasia, these lesions rarely cause complete occlusion thus contrasting with atherosclerotic disease.

Table 5.

A: INTRINSIC LESIONS
1. Aneurysm (Cummings: J Urol 102:144, 1973)
2. Emboli (Arakawa: Arch Intern Med 129:958, 1973)
3. Arteritis
   Polyarteritis nodosa (Dornfield: JAMA 215:1950, 1971)
   Takayasu's (Kirshbaum: Am Heart J 80:811, 1970)
4. Arteriovenous fistula (Oxman: Mayo Clin Proc 48:207, 1973)
5. Angioma (Ferreras-Valenti: Am J Med 39:355, 1965)
6. Neurofibromatosis (Schurch: CMAJ 113:879, 1957)
7. Tumor thrombus (Jennings: Br Med J 2:1053, 1964)
8. Rejection of renal transplant (Gunnels: N Engl J Med 274:543, 1966)
9. Thrombosis after umbilical arter catheterization (Plumber: J Pediatr 89;802, 1976)
10. Surgical ligation of renal artery (McCormack: Arch Surg 198:220, 1974)
11. Traumatic Occlusion (Knorring: Lancet 1:934, 1976)
12. Radiation (Staab: Am J Roentgenol 126:634, 1976)
13. Intrarenal cyst (Babka: N Engl J Med 291:343, 1974)
14. Congenital unilateral renal hypoplasia (Ask-Upmark kidney) (Rosenfeld: Br Med J 2:217, 1973)
15. Unilateral renal infection (Marks: Am J Surg 121:35, 1971)

B: EXTRINSIC LESIONS
1. Pheochromocytoma (Raghavaiah: J Urol 116:243, 1976)
2. Congenital fibrous band (Silver: Ann Surg 183:161, 1976)
3. Pressure from diaphragmatic crus (Martin: Am J Surg 121:35, 1971)
4. Metastatic tumors (Weidmann: Am J Med 47:528, 1969)
5. Subcapsular or perirenal hematoma (Sparks: Arch Intern Med 136:1097, 1976)
6. Retroperitoneal fibrosis (Castle: JAMA 225:1085, 1973)
7. Ptosis (Derrick: Am J Surg 106:673, 1963; Zeeuw: Lancet 1:125, 1977)
8. Ureteral obstruction (Nemoy: JAMA 225:512, 1973)

In addition to the most common renal arterial lesions described above, certain other disorders have been known to cause renal artery obstruction (Table 5).

VIII. CLINICAL FEATURES

From the clinical cumulative experience gained from several centers, the seemingly uniform conclusion is that little or no distinguishing clinical features exist to separate renovascular from essential hypertension. It is this lack of specific clinical characteristics that led to the application of several screening procedures to distinguish primary from renovascular hypertension. Clinical definition of renovascular hypertension is also hampered by the occurrence of renal artery stenosis in patients with essential hypertension and in normotensive individuals. The diagnosis of renovascular hypertension requires not only the anatomic demonstration of renal artery stenosis but also evidence that the noted abnormality is indeed contributing to patient's hypertension which can be cured or improved by the relief of ischemia. Ironically, pre-operative diagnosis is often imperfect despite the availability of several screening and diagnostic procedures. Except for characteristic abdominal bruit, there is no single clinical manifestation of renovascular hypertension that reliably distinguishes it from essential hypertension. Certain clinical manifestations, however, should permit a high degree of suspicion to select patients for work-up.

A comparison of clinical features of renovascular hypertension and essential hypertension from the published reports can be misleading. The controls (essential hypertension) in these studies were chosen because of negative renal arteriograms. However, they may have been selected for angiography because of complicated or atypical hypertension. Conversely, some patients with renovascular hypertension may have been missed because of absence of any particular clinical features. Moreover, renovascular hypertension is not a homogenous entity. It encompasses two distinct pathological entities - atherosclerosis and fibromuscular dysplasia - with different age and sex characteristics. Generally atherosclerotic renal artery stenosis is likely to occur in patients 50 years or older, whereas, fibromuscular dysplasia is commonly diagnosed in females under 40 years.

The decision to consider work-up for renovascular hypertension begins with the identification of patients who are at high risk for renovascular hypertension. The Co-operative Study of Renovascular Hypertension collected data on close to 2500 patients with hypertension (Simon et al, 1972). Of these, 175 (7%) had proven renovascular hypertension. The clinical differences between patients with renovascular hypertension and those with essential hypertension were considered to be quantitative rather than truly qualitative. This is the best demographic study on renovascular hypertension to date. Despite the observation that patients with renovascular hypertension are more likely to be Caucasians with short duration of hypertension, lacking family history of hypertension, one of the conclusions of the Co-operative Study was that there are no "distinctive" features of renovascular hypertension.

Table 6: Clinical Characteristics of Essential Hypertension and Renovascular Hypertension Cured by Surgery*

	Essential Hypertension, %	Renovascular Hypertension, %
Duration of hypertension		
< 1 yr	12	24
> 10 yr	15	6
Age of onset (>50 yr)	9	15
Family history of hypertension	71	46
Fundi (grade 3 or 4)	7	15
Bruit		
Abdomen	9	46
Flank	1	12
Abdomen or flank	9	48
BUN (>20 mg/100 ml)	8	15
Serum K (<3.4 mEq/liter)	8	16
Serum CO_2 (>30 mEq/liter)	5	17
Urinary casts	9	20
Proteinuria (trace or more)	32	46

*131 cases in each group, matched by age, sex, race, and diastolic blood pressure. Only the statistically significant differences are presented. (From: Simon N et al, JAMA 1972;220:1209-18).

Table 7: Clinical characteristics of essential and renovascular hypertension in 64 matched pairs cured by an operation*

	Hypertension	
	Essential	Renovascular
Duration of hypertension (%):		
< 1 yr.	10	25
> 10 yrs.	17	6
Age at onset > 50 yrs.	8	17
Family history of hypertension	70	40
Fundi grade III or IV	7	15
Bruit	7	48

*Patients matched by age, sex, race and diastolic blood pressure. (From Kaufman JJ: J Urol 1979;121:139-44)

The characteristics of renal vascular hypertension overlap with essential hypertension. Abdominal bruit noted in 48% of cases in the Co-operative Study is probably the single most valuable physical finding in renovascular hypertension. It's diagnostic value, however, is limited by the detection of a bruit in patients with essential hypertension. In

older patients abdominal bruits may occur as a result of multiple abdominal arterial stenosis (Novick, 1981). Patients with renovascular hypertension tend to have more advanced retinopathy compared to patients with essential hypertension (Hunt et al, 1974). While not sufficiently discriminating, it is necessary to review clinical attributes of renovascular hypertension.

A. AGE

Fibromuscular dysplasia of the renal artery is typically diagnosed in children and young adults, whereas, atherosclerotic lesions are diagnosed in the middle aged and elderly patients. The average age of patients with fibrous dysplasia is considerably less than that of patients with atherosclerosis (Simon et al, 1972). Fibrous dysplasia has been reported in infancy (Stabb et al, 1976). In the Co-operative Study, atherosclerotic disease of renal arteries was diagnosed before age 20 in 2 of 80 patients.

The average age of patients with essential hypertension in the Co-operative Study was 35 years and it was 32.6 years for patients with fibrous dysplasia. The average age for the atherosclerotic group was 46 years.

In general, renovascular hypertension due to fibromuscular dysplasia is likely to be diagnosed in females under 40 years, whereas atherosclerotic lesions dominate in males over 50 years but many exceptions are seen depending on the time at which arteriogram is performed.

B. FAMILIAL OCCURRENCE

There are a number of reports pointing to the familial occurrence of fibrous dysplasias (Assendfelt et al, 1973; Hansen et al, 1965; Morimoto et al, 1976; Major et al, 1977). The exact mode of transmission of the disorder is not known. Even in the familial pattern, females appear to be more frequently affected than males.

C. RACE

Although there is general belief that renovascular disease is uncommon in blacks (Gifford and Simon et al, 1972; Capelli et al, 1973, Foster et al, 1969; Hall and Grim et al, 1979; Keith, 1982), this subject should now be reconsidered with the newly available improved diagnostic tests.

In the Co-operative Study of Renovascular Hypertension, blacks constituted 7% of patients with atherosclerotic disease and 10% of patients with fibromuscular dysplasia. Foster and colleagues at Vanderbilt diagnosed renal artery stenosis in 13 of 81 black patients undergoing extensive evaluation, whereas, 53 of 127 white patients had renovascular disease. Functional studies revealed that the lesions were significant in 5 of the 13 blacks (38.5%) versus 39 of 53 whites (73.6%). An additional study from the same institution (Davis et al, 1979)

investigated for the presence of renal artery stenosis in patients with accelerated or malignant hypertension and noted that renal artery stenosis was six times more frequent among the whites.

The Indiana University group (Grim et al, 1979) found functional renal artery stenosis in 44 of 377 hypertensive whites (11.7%) but in none of the 87 hypertensive blacks. Perhaps the largest series of cases of renovascular hypertension in blacks was compiled by Keith (Keith, 1982). During a 10 year period, 47 cases of renovascular hypertension were detected from 7200 hypertensive blacks. It has been reported by Vetrovec and colleagues that 30% of blacks with significant coronary disease had concomitant renal artery stenosis (Vetrovec et al, 1983). This correlation between coronary artery diseases and renal artery stenosis is not surprising since both the processes share common risk factors - hypercholesterolemia, smoking, and diabetes mellitus. The apparent higher stenosis in hypertensive black women as compared to hypertensive black men is interesting with regard to higher prevalence of hypercholesterolemia and diabetes in older black women as compared with black men (Deubner et al, 1980; National Center for Health Statistics, 1978). The inference that renovascular hypertension is uncommon in blacks is subject to debate and open to a multitude of interpretations.

D. SEX

As mentioned elsewhere, females predominate among patients with fibromuscular dysplasia, whereas atherosclerotic lesions are more prevalent among males. In most large series 75-80% of patients with fibromuscular dysplasia were females, whereas about two-thirds of patients with atherosclerotic disease were males. The role of hormonal influences in predisposing women to arterial dysplasias has not been delineated. The results of therapy are not influenced by gender.

E. OBESITY

Obesity was more prevalent in patients with essential hypertension then in patients with renovascular hypertension in the Co-operative Study. Clinical experience suggests that patients with fibrous dysplasia tend to be thin.

F. SMOKING

Cigarette smoking has been proposed as an etiological factor in fibromuscular dysplasia (Sang et al, 1987). This factor has not been carefully analyzed in the larger series.

G. CLINICAL CHARACTERISTICS

Compared to essential hypertension, renovascular hypertension is decidedly uncommon but the clinical distinction between these two entities is not striking. Except for a systolic/diastolic bruit, there is no other single criterion that can reliably distinguish renovascular hypertension from essential hypertension.

DURATION OF HYPERTENSION

In general, the duration of hypertension is shorter for patients with renovascular hypertension than for patients with essential hypertension. Duration of hypertension is an important prognostic factor. It has been suggested that the results of surgical treatment are inversely proportional to the duration of renovascular hypertension (Hughes et al, 1981; Simon et al, 1972). In the Co-operative Study best surgical results were obtained in patients whose hypertension was of less than 2 years duration before the operation.

CONCOMITANT VASCULAR DISEASE

Not surprisingly, vascular complications such as myocardial infarction, stroke, etc. occur more frequently in patients with atherosclerotic renovascular disease. Obviously, the presence of extra-renal vascular disease alters the ultimate outcome of patients with renovascular hypertension. No such relationship to surgical outcome has been found in patients with fibromuscular dysplasia.

DRUG RESISTANT HYPERTENSION

Most of the large series including the Co-operative Study have not addressed the responsiveness of renovascular hypertension to medical treatment. In my experience, many patients with renovascular hypertension demonstrate resistance to drug therapy. Hunt and colleagues have noted that a majority of patients with renovascular hypertension do not respond satisfactorily to medical treatment. Resistant hypertension, therefore, is an indication for work-up to exclude renovascular hypertension. A less severe form of hypertension does not exclude the possibility of renovascular hypertension.

Table 8: RENOVASCULAR HYPERTENSION IN PATIENTS WITH MALIGNANT HYPERTENSION. (From Davis BA, Crook JE, Vestal RE, et al.: N Engl J Med 301:1273, 1979).

NO. OF PATIENTS	RENAL ARTERY STENOSIS	RENOVASCULAR HYPERTENSION
123	43 (35%)	28 (23%)

ACCELERATED/MALIGNANT HYPERTENSION

Accelerated/malignant hypertension is a common presentation of renovascular hypertension (Simon et al, 1972; Davis et al, 1979). Rapid onset or progression of hypertension associated with severe funduscopic changes is a valuable clue to the presence of renal artery stenosis. Davis et al, detected renovascular hypertension in 23% of 123 patients with severe hypertension and Grade III or IV funduscopic retinal changes

(Table 8). This is considerably higher than the prevalence of renovascular hypertension among the general hypertensive population and argues for aggressive work-up in patients with accelerated/malignant hypertension.

Contrary to the commonly held notion, hypertensive diabetics do not have a higher incidence of renovascular hypertension (Munichoodapa et al, 1979; Working Group, 1987).

DETERIORATION OF RENAL FUNCTION WITH ANGIOTENSIN CONVERTING ENZYME INHIBITION

Rapid deterioration of renal function after treatment with a converting enzyme inhibitor strongly suggests bilateral renal arterial disease or renal artery stenosis of a solitary kidney (Bender et al, 1984). Transient loss of renal function can also be provoked by converting enzyme inhibition in patients with unilateral renal artery stenosis (Wenting et al, 1984). The mechanism of this derangement will be discussed under the medical treatment section. Another indication may be added for the work-up of renovascular hypertension - rapid decline in renal function following treatment with ACE inhibitors.

HEMATURIA/FLANK PAIN

While flank pain and or hematuria due to renal infarction can denote the presence of renal artery stenosis, these symptoms are uncommon.

TRAUMATIC INJURY

Hypertension following traumatic injury to renal vasculature is an indication to exclude renal artery occlusion.

PHYSICAL FINDINGS

BLOOD PRESSURE: Like in essential hypertension, the hypertension in patients with renovascular hypertension can be of any degree. As alluded to earlier, severe hypertension, accelerated/malignant hypertension and refractory hypertension are not uncommon manifestations of renovascular hypertension. In fact, severe resistant hypertension is a common indication for the work-up of renovascular hypertension.

OPTIC FUNDUS

In the Co-operative Study, hypertensive retinopathy - Grade III (exudates, hemorrhages as Grade IV (papilledema) - occurred twice often in renovascular patients compared to patients with essential hypertension. Similarly, nearly 25% of patients with these funduscopic findings turned out to have renovascular hypertension (Davis et al, 1979).

The mere presence of severe retinal arteriolar spasm without additional findings indicates severe or recent onset of hypertension which may signify a renovascular etiology. The Mayo group reported that a significant proportion of patients with renovascular hypertension had this so called arterioplastic retinopathy (Hunt et al, 1974).

ABDOMINAL BRUIT

A bruit is produced when blood flow in an artery is turbulent instead of being laminar or when blood flows through a tortuous or narrowed artery. Detection of an abdominal bruit while not diagnostic strongly suggests renovascular disease. The characteristic finding in renovascular hypertension is the continuous, high pitched abdominal murmur which occurs in at least a third of patients with renovascular disease (Eipper et al, 1976). The helpfulness of a carefully elicited abdominal bruit in the diagnosis of renovascular hypertension has been stressed by several authors (Simon et al, 1972; Honari et al, 1971; Maxwell et al, 1966; Brest, 1968). The classical bruit radiates from the epigastrium to the upper quadrant of the side of renal artery stenosis. The presence of a diastolic component adds to the significance of a bruit. When carefully elicited a characteristic abdominal bruit is heard in patients with atherosclerotic renal artery stenosis as well as in those with fibromuscular dysplasia (Table 9). At the Cleveland Clinic, the characterization of bruit had some prognostic importance (Table 10) but other centers have not reported this phenomenon.

Table 9: Clinical Features in 87 Patients With Unilateral Renal Arterial Stenosis

	Bruit		No Bruit	
	Fibrous Disease	Athero-sclerosis	Fibrous Disease	Athero-sclerosis
Mean age (yr)	36.9	54.5	34.0	49.9
Sex (no. of patients)				
Male	3	10	3	17
Female	33	4	8	9
Average BP				
Systolic	177	191	177	184
Diastolic	110	111	116	110
Duration of hypertenion (no. of patients)				
1 year	12	5	4	7
1.1 to 3 years	13 } 70%	2 } 58%	1 } 55%	4 } 44%
3.1 to 5 years	3	4	1	5
5.1 to 10 years	6	...	1	4
10 years	2	1	2	5

BP = blood pressure (mm Hg).
(From Eipper DF et al: Am J Cardiol 1976;37:48-52)

In the Co-operative Study the presence of an abdominal bruit was a discriminatory feature in patients with renovascular hypertension. By using the presence of a bruit along with other clinical criteria, Moser and Caldwell detected

renovascular disease in 33 of 50 patients (Moser and Caldwell, 1962). Pure systolic bruits offer no diagnostic value and the presence of diastolic component strongly indicates renovascular disease (Hunt et al, 1974). The presence of a diastolic component also lends a favorable prognosis in patients with fibromuscular dysplasia (Eipper et al, 1976). In general, characteristic bruits of renovascular origin are heard more often in patients with fibromuscular disease compared to those with atherosclerotic disease. While the presence of a typical bruit is helpful when detected, its absence does not exclude renal artery stenosis. In contrast to the bruit of renovascular origin which is usually heard in the epigastrium and often radiates to one or both flanks, in celiac stenosis the bruit is localized to a small area in the midepigastric (McLoughlin et al, 1975). It should be pointed out that abdominal bruits perhaps signifying generalized vascular disease are more likely to occur in patients who smoke compared to non-smokers (Niarchos et al, 1986).

Table 10: Relation of Systolic-Diastolic Bruit and Short Duration of Hypertension to Favorable Surgical Result

	Favorable Surgical Result (no. of patients)	
	Fibrous Disease	Athero-sclerosis
Total	33/47 (70%)	16/40 (40%)
S-D bruit	21/25 (84%)	1/5 (20%)
Duration of hypertension < 3 years		
Total	26/32 (81%)	12/20 (60%)
Without S-D bruit	9/14 (64%)	11/17 (64%)
With S-D bruit	17/18 (94%)	1/3 (33%)

S-D = systolic-diastolic.
(From Eipper DF et al: Am J Cardiol 1976;37:48-52)

HOW TO LISTEN FOR THE ABDOMINAL BRUIT?

The patient should be in a supine position with knees flexed and the abdomen relaxed. Place the diaphragm of the stethoscope below the xiphoid process and press down with the palm of the hand until the stethoscope head indents the skin. Advance the stethoscope along one subcostal margin and then the other. The continuous or systolic/diastolic blowing murmur of renal artery stenosis will be louder in systole, tapering off into diastole. The murmurs may not be loud, so the auscultation should be performed in quiet atmosphere. Detecting the first murmur of renal artery stenosis makes the subsequent ones much easier to appreciate.

Table 11: Clinical Clues Suggesting Renovascular Hypertension

Systolic/diastolic epigastric, subcostal, or flank bruit
Accelerated or malignant hypertension
Unilateral small kidney discovered by any clinical study
Severe hypertension in child or young adult, or after age 50 years
Sudden development or worsening of hypertension at any age
Hypertension and unexplained impairment of renal function
Sudden worsening of renal function in hypertensive patient
Hypertension refractory to appropriate three-drug regimen
Impairment in renal function in response to angiotensin-converting enzyme inhibitor
Extensive occlusive disease in coronary, cerebral, and peripheral circulation

The indications for the work-up of renovascular hypertension are listed in Table 11. Obviously, the occurrence of more than one of the clue enhances the chances of finding renovascular hypertension. Conversely, it must be appreciated that renovascular hypertension may be present without any clinical clue.

The typical patient with renovascular hypertension due to atherosclerotic disease is a 60 year old make with difficult-to-treat hypertension or new onset hypertension with a blood pressure of 230/130 mm Hg.

The typical patient with fibromuscular dysplasia is a 25 year old woman with new onset hypertension who presents with a blood pressure of 180/130 mm Hg, headache, and a continuous abdominal bruit.

Unfortunately, only a fraction of patients with renovascular hypertension will present in such a characteristic fashion. Many behave like those with essential hypertension. The physician must exercise proper clinical judgement to decide when and how to consider evaluation for remediable renovascular hypertension.

IX. SCREENING TESTS

For a condition such as renovascular hypertension which does not exhibit distinct diagnostic clinical features, careful screening of patients is necessary to accomplish a cost effective work-up. Ideally a screening test should be simple, safe, inexpensive, sensitive, and specific. None of the presently available screening tests meets these criteria. Each has its limitations. Nevertheless, when used properly, these tests provide the basis for performing arteriography in patients suspected of renovascular hypertension.

Table 12: SCREENING STUDIES

1. PERIPHERAL PRA
2. RAPID SEQUENCE IVP
3. RENOGRAM/SCINTIGRAPHY

Table 13: Diagnostic Accuracy of the Intravenous Pyelogram

Reference	Patients with essential hypertension		Patients with renovascular hypertension	
	No. of cases	% Abnormal	No. of cases	% Abnormal
Cooperative Study: JAMA 220:1218, 1972	771	11.4	138	83.0
Maxwell: New Engl J Med 270:213, 1964	221	17.0	42	93.0
Wilson: Arch Intern Med 112:270, 1963	127	8.0	128	72.0

(From Bookstein JJ, et al: JAMA 220:1218, 1972.

A. INTRAVENOUS PYELOGRAPHY (IVP)

This procedure became an acceptable test for renovascular hypertension after Maxwell and colleagues described the radiographic features suggestive of renal artery stenosis (Maxwell et al, 1964). Its initial popularity can be attributed to simplicity and safety as demonstrated in the Co-operative Study. The hypertensive IVP was found to be a useful screening test in the Co-operative Study (Bookstein et al, 1972a, 1972b) (Table 13). For many years, we relied on the hypertensive (rapid-sequence) IVP alone to screen patients for renovascular hypertension. However, recent analysis of this procedure has convincingly shown that it is not a satisfactory screening test (Thornbury et al, 1982). The major criteria for the diagnosis of renal artery stenosis on an IVP are the following:

1) Disparity in kidney size: The right kidney may normally appear to be 1.0-1.5 cm shorter than the left due to rotation by the liver. Keeping this margin for calculation, diminished renal length (right more than 2 cm less than the left, or left more than 1.5 cm less than right) is suggestive of unilateral renal ischemia.

2) Delayed appearance time: A discrepancy in the calyceal appearance time of at least one or more minutes is indicative of renal ischemia.

3) Hyperconcentration of the dye on the ischemic side: Hyperconcentration of contrast material within the collecting system of the ischemic kidney when compared to the normal kidney may be detected on late films. This is due to greater resorption of sodium and water causing a relative increase in the density of non-absorbable contrast material.

4) Other urographic features compatible with renal ischemia which are not seen commonly include parenchymal atrophy, ureteral notchings, and a decreased collecting system volume with narrowed calyces on the ischemic side.

Technique of performing a hypertensive IVP. Intravenous contrast material (50-100 ml) bolus is injected over 15 to 30 seconds. The exact amount of iodinated contrast depends on the renal function. Films are taken at 1, 2, 3, 4, 5, 10, and 15 minutes to determine renal size, density, and calyceal appearance time of contrast material. A late film at 30 minutes is useful for assessment of contrast material.

CURRENT STATUS OF IVP AS A SCREENING PROCEDURE

The usefulness of IVP as a screening test for renovascular hypertension seemed initially promising. The true positive results were noted in 90-93 percent of patients with unilateral renal artery stenosis (Correa et al, 1962; Maxwell et al, 1964). However, subsequent experience has revealed low sensitivity of the IVP to detect renal artery stenosis. A false negative test rate ranging from 22 to 58% has been reported (Pollack and Banner, 1985; Thornbury et al, 1982; Lalli, 1981). Not all observers are disenchanted with IVP. Some still believe that when carefully performed and interpreted, a hypertensive IVP may have a role in screening for renovascular hypertension (Havey et al, 1985).

With extensive analysis of their data, the Co-operative Study group concluded that in the diagnosis of unilateral renal artery stenosis, hypertensive IVP had a 10.3% false positive rate, i.e. abnormal IVP in patients subsequently not found to have renal artery stenosis and a false negative rate of 1.7%, i.e. normal hypertensive IVP in patients subsequently found to have renovascular hypertension. Based on these figures the rapid sequence IVP was recommended as a useful screening test However, wide-spread clinical experience suggested otherwise and more recent studies suggest an unacceptable false negative rate.

Table 14: Surgical Outcome vs. Hypertensive Urogram Result. (From: Thornbury JR et al: Am J Roentgen 1982:138:43-9)

Type of Renal Artery Stenosis/ Surgical Outcome	No Patients	(%)	Urogram Positive, no.	(%)	Urogram Negative, no.	(%)
Fibrodysplastic unilateral:						
Cured	60	(55.6)	35	(58.3)	25	(41.7)
Improved	45	(41.7)	17	(37.8)	28	(62.2)
Failure	3	(2.8)	0		3	(100.0)
Subtotal	108	(100.0)	52	(48.1)	56	(51.9)
Focal arteriosclerotic:						
Cured	15	(31.3)	12	(80.0)	3	(20.0)
Improved	29	(60.4)	20	(69.0)	9	(31.0)
Failure	4	(8.3)	2	(50.0)	2	(50.0)
Subtotal	48	(100.0)	34	(70.8)	14	(29.2)
Overt, generalized arteriosclerotic:						
Cured	10	(24.4)	8	(80.0)	2	(20.0)
Improved	22	(53.7)	17	(77.3)	5	(22.7)
Failure	9	(21.9)	4	(44.4)	5	(55.6)
Subtotal	41	(100.0)	29	(70.7)	12	(29.3)
Totals:						
Cured	85	(43.2)	55	(64.7)	30	(35.3)
Improved	96	(48.7)	54	(56.3)	42	(43.8)
Failure	16	(8.1)	6	(37.5)	10	(62.5)
Grand total	197	(100.0)	115	(58.4)	82	(41.6)

Table 15: Regrouping Cooperative Study Data to Compute False-Negative and False-Positive Rates. (Data from Thornbury JR et al: Am J Roentgen 1982138:43-9).

Renal Artery Stenosis	Urogram		Total
	Abnormal (positive)	Normal (negative)	
Unilateral, 50% or greater occlusion	225	63	288
Less than 50% occlusion or essential hypertension	116	781	897
	No.		%
True-positive rate (sensitivity)	225/288		78.1
False-positive rate	116/897		12.9
True-negative rate (specificity)	781/897		87.1
False-negative rate	63/288		21.9

Thornbury and colleagues, from their vast experience at the University of Michigan, showed that the diagnosis of significant renovascular disease was missed on urography in 41.6% of patients (Thornbury et al, 1982). These authors have challenged the conclusions of the Co-operative Study (Table 14 and 15). The data reported by the Co-operative Study group were based on the hypothetical 10% prevalence of renovascular hypertension. Thornbury and colleagues, pointing out the calculation errors, have reanalyzed the Co-operative data and discovered a false negative rate of 21.8% rather than 1.7% as reported earlier. The diagnostic yield of an IVP in patients with bilateral renovascular disease is substantially low. The test also yields a high percentage of false negatives (42%) in children with renovascular hypertension (Lawson et al, 1977). On the basis of these data, a hypertensive IVP is not a reliable screening test to diagnose renovascular hypertension. Certainly its indiscriminate use as a routine investigation in patients with hypertension is unjustified.

B. ISOTOPE RENOGRAPHY

Radionuclide imaging of the kidneys is a non-invasive method of assessing of renal ischemia. Using a renally cleared radiolabelled substance ^{123}I-hippuran, ^{99m}Tc-DTPA (technetium) (cleared by filtration), a gamma scintillation camera, and computer assistance, qualitative and quantitative renal function can be measured (Cheruvu and Blaufox, 1982). Past experience has shown its usefulness to be similar to that of hypertensive urography in its false negative rate. Recent advances in the imaging techniques and improved computer-derived analysis have led to a renewed interest in its application to diagnose renal perfusion abnormalities. Two indices of renal perfusion - effective renal plasma flow and renal function (renogram) - can be obtained with radioisotopic studies.

Effective Renal Plasma Flow. The renal plasma flow can only be estimated indirectly with the non-invasive technique. This is calculated on certain assumptions. If an ideal substance has an extraction efficiency of 100%, then its clearance should be equal to renal plasma flow. Hippuran has an extraction efficiency of 90% and its clearance is used to get approximate renal plasma flow (Velchik, 1985; Lingardh, 1972). Para-aminohippuric acid (PAH) is currently the compound of choice for the estimation of renal plasma flow which is calculated by the following formula:

$$1)\quad ER = \frac{A - V}{A}$$

ER = extraction ratio, A = arterial concentration of the agent, V = venous concentration of the agent. If the clearance of the substance and its extraction ratio are known, effective renal plasma flow can be calculated.

$$2)\quad \text{Renal plasma flow} = \text{Clearance} \times \frac{1}{ER}$$

Technetium labelled compounds are used to estimate glomerular filtration rate (GFR). ^{99m}Tc has ideal physical characteristics by virtue of its short half-life and radiation properties.

RENOGRAM

A renogram is a time activity curve of renal function since its records the passage of a radiopharmaceutical through the kidney (Figure 9). It is an index of renal blood flow, GFR, and tubular function (Blaufox and Bell, 1976; Blaufox and Freeman, 1980; Velchik, 1985). I-131 Hippuran is the radiopharmaceutical of choice for renographic studies because of its high extraction ratio and sensitivity to changes in renal function. Basically, a renogram consists of three phases: 1) the vascular phase; 2) the tubular phase; and 3) excretory phase. The first phase, lasting approximately 1 minute, represents the initial tracer uptake by the kidney and is seen by the rapid slope or spike activity. During the second phase, a more gradual rise in activity occurs to peak at 3 to 5 minutes after the injection. In this phase, the initial vascular activity declines to be replaced by activity in the parenchyma. In the final phase, there is a progressive decrease in activity as washout occurs from the renal tubules and parenchyma. This phase is significantly affected by the urine flow rate.

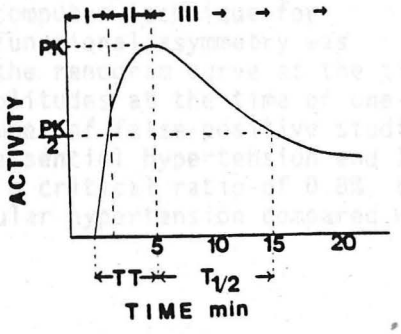


Figure 9: Renogram: I = vascular or blood pool phase; II = parenchymal or tubular phase; III = excretory or washout phase (TT = transit time; $T_{1/2}$ = the time from peak activity to 1/2 peak activity; PK = peak activity). (From Velchik MG: Urol Clin N Amer 1985;12:603-31).

Table 16: Probability of Essential Hypertension or Renovascular Hypertension on the Basis of Screening Procedures

	Essential hypertension (%)	Renovascular hypertension (%)
No abnormality	99	1
Abdominal bruit present	61	39
Abnormal IVP	48	52
Abnormal renogram	74	26
Abnormal IVP and renogram	30	70
Abnormal IVP and renogram, and abdominal bruit present	4	96

In the earlier clinical experience, radionuclide renogram has been suggested as a simple and safe screening procedure yielding a high incidence (85%) of positive results (Sharpe et al, 1966; Winter, 1963). However, additional reports cited a high degree of false positivity decreasing the specificity of the test (Sandler and Rickards, 1966; Doig et al, 1963). The quantitative data are calculated by determining the rate of accumulation and clearance of radiolabelled substance by the kidney. Renal artery stenosis prolongs the time to peak but some non-vascular disorders such as low urine flow and renal tubular disorders also may show similar abnormalities (Farmelant and Burrows, 1974). The Co-operative Study results show that the reliability of an abnormal renogram is enhanced when other tests are also abnormal (Table 16).

As a technique for screening renovascular disease, the sensitivity of isotope renography has been variable - 80% (Kaufman, 1979), 85% (McAfee et al, 1977), and 79% (Maxwell et al, 1968). The specificity also varied - 81% (Maxwell and Varady, 1976), 75% (McAfee et al, 1977), and 74% (Kaufman, 1979). While probably more sensitive than IVP, a renogram may be less specific as judged from the experience in 60s and 70s. What then were the sources of error in the interpretation of isotope renogram? Since the uptake slope is made up of rate of isotope appearance and to a minor extent, the early phase of excretion, kidneys with poor excretory function or with high peripheral resistance to flow may have an abnormal slope without there being actual diminution of renal blood flow. The interpretation is based on isotope uptake and disappearance from the kidneys, thus compounding the source of error. Bilateral renal artery stenoses may contribute to a false negative scan. Analyzing the earlier experience, Dean concluded that like the rapid sequence of IVP, renogram suffers from an unacceptable (25%) incidence of false results (Dean, 1985). In order to minimize several variables, the Co-operative Study used a computer technique for quantitative analysis of renograms. An index of functional asymmetry was obtained by comparing the ratio of amplitudes of the renogram curve at the time of initial peak (Tmax) divided by the ratio of amplitudes at the time of one-half its maximal value (T 1/2max) which limited the number of false-positive studies. This technique was compared in 152 patients with essential hypertension and 164 patients with proven renovascular disease. Using a critical ratio of 0.8%, there were 90% abnormal scans in patients with renovascular hypertension compared with 10% abnormal studies in essential hypertension.

McNeil et al evaluated the comparative merits of IVP and renography as a screening procedure for renovascular hypertension (McNeil et al, 1975). They found renography to be superior to IVP - true positivity being 85% versus 78%. Similarly, another comparative analysis revealed modest superiority of renography over IVP in sensitivity and specificity (Farmelant et al, 1964). Keep in mind that these evaluations were performed before the advent of improved computerized quantitative gamma camera renography. Techniques to measure parenchymal transit times by deconvolutional analysis have enhanced the specificity of the procedure.

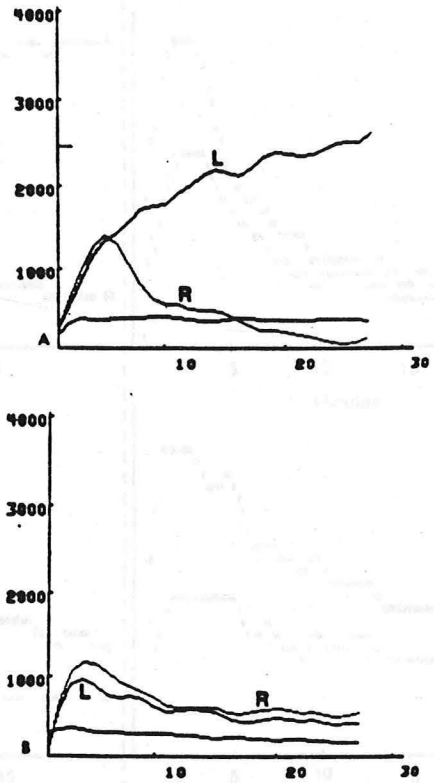


Figure 10: Abnormal renogram suggesting left renal ischemia (top) and improvement in the renographic appearance following the correction of left renal artery stenosis (bottom).

When considering isotope renography as a screening tool, certain inherent features should be kept in mind (Bretille, 1985).

1) Retention time abnormalities are less sensitive but they are rare in the absence of other pathologic entities (Benedetti-Valetini et al, 1978; Friedland et al, 1983).

2) Flow asymmetry while denoting an abnormality is not sensitive by itself. Its significance is enhanced in the presence of a renin-producing kidney.

3) The combination of flow asymmetry and/or retention time abnormality seem to be more sensitive.

4) In the presence of bilateral vascular lesions or other renal diseases, the renogram is not helpful (McAfee et al, 1977; Von Otto et al, 1980).

In summary, isotope renography techniques have improved considerably in the last decade. However, the test is not perfect to screen patients for renovascular hypertension. Assuming a sensitivity of 90% and a specificity of 80%, the predictive value would only be 33% given the infrequency of renovascular hypertension amongst the hypertensive population. If one uses the test in patients strongly suspected of having renovascular hypertension, the most valuable result would be a negative test with a negative predictive value of 98%.

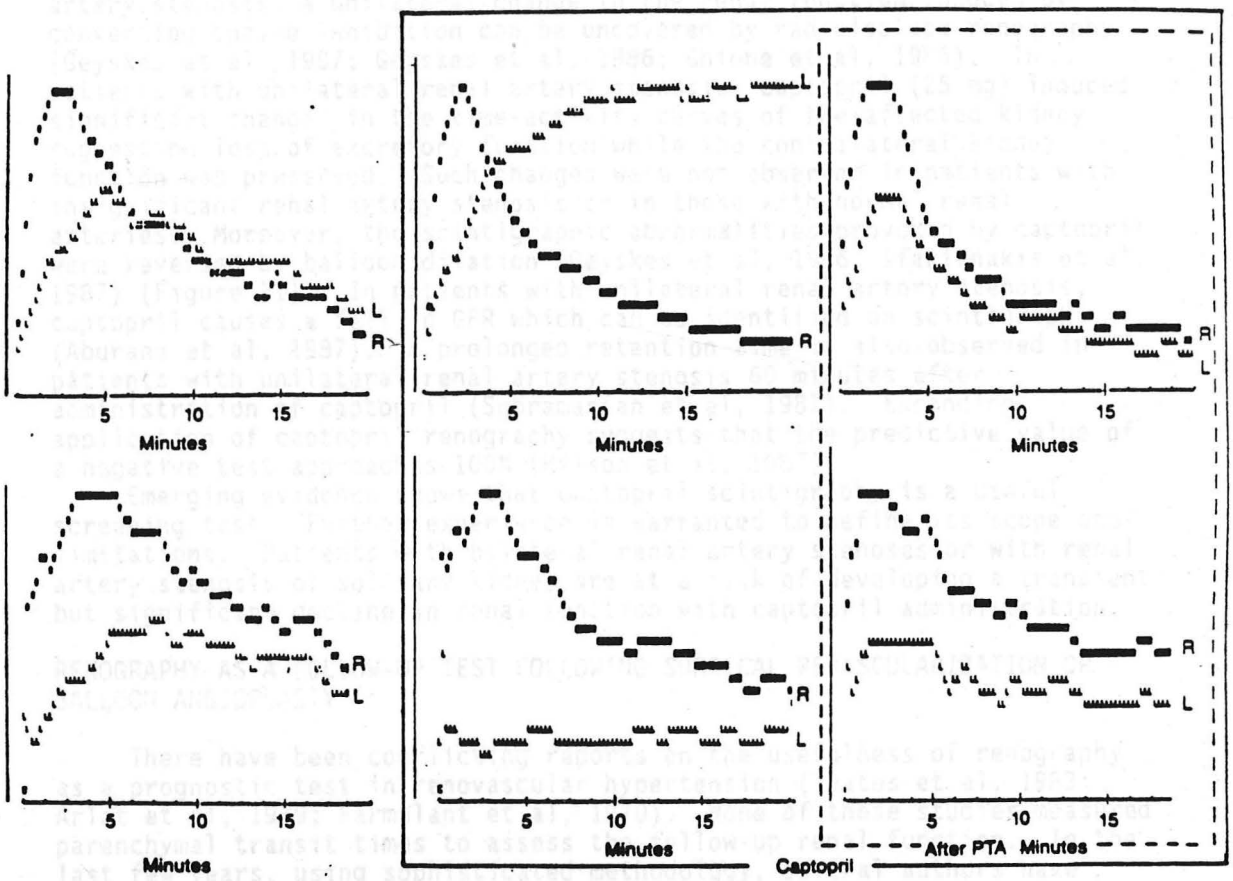


Figure 11: Top, From left to right, orthoiodohippurate sodium I 131 renography curves before percutaneous transluminal angioplasty (PTA) without and with captopril premedication and after PTA with captopril premedicatin. Bottom, Technetium Tc 99m diethylenetriamine pentracetic acid curves made at identical times and conditions. R indicates right; L, left. (From Geyskes GG et al: Arch Intern Med 1986;146:1707).

RENOGRAPHY WITH CAPTOPRIL

It has been demonstrated that a kidney with renal artery stenosis may exhibit impaired function during converting enzyme inhibition (Silas et al, 1983; Curtis et al, 1983; Hricik et al, 1983). This phenomenon was mainly observed in patients with bilateral renal artery stenosis or in

patients with arterial stenosis of a solitary kidney and is thought to be due to disruption of the autoregulation of GFR, which becomes dependent on angiotensin II under conditions of low perfusion pressure (Blythe, 1983). Although a decline in GFR can be induced by converting enzyme inhibition in the affected kidney of patients with unilateral renal artery stenosis, the overall renal function is preserved by the contralateral kidney. Recently, it has been demonstrated in patients with unilateral renal artery stenosis, a unilateral change in the renal function induced by converting enzyme inhibition can be uncovered by radioisotope renography (Geyskes et al, 1987; Geyskes et al, 1986; Ghione et al, 1986). In patients with unilateral renal artery stenosis, captopril (25 mg) induced significant changes in the time-activity curves of the affected kidney suggesting loss of excretory function while the contralateral kidney function was preserved. Such changes were not observed in patients with insignificant renal artery stenosis or in those with normal renal arteries. Moreover, the scintigraphic abnormalities provoked by captopril were reversed by balloon dilation (Geyskes et al, 1986; Sfakianakis et al, 1987) (Figure 11). In patients with unilateral renal artery stenosis, captopril causes a fall in GFR which can be identified on scintigraphy (Aburano et al, 1987). A prolonged retention time is also observed in patients with unilateral renal artery stenosis 60 minutes after administration of captopril (Subramanian et al, 1987). Expanding application of captopril renography suggests that the predictive value of a negative test approaches 100% (Hilson et al, 1987).

Emerging evidence shows that captopril scintigraphy is a useful screening test. Further experience is warranted to define its scope and limitations. Patients with bilateral renal artery stenoses or with renal artery stenosis of solitary kidney are at a risk of developing a transient but significant decline in renal function with captopril administration.

RENOGRAPHY AS A FOLLOW-UP TEST FOLLOWING SURGICAL REVASCULARIZATION OR BALLOON ANGIOPLASTY

There have been conflicting reports on the usefulness of renography as a prognostic test in renovascular hypertension (Teates et al, 1983; Arlat et al, 1979; Farmelant et al, 1970). None of these studies measured parenchymal transit times to assess the follow-up renal function. In the last few years, using sophisticated methodology, several authors have reported that quantitative renography is an excellent non-invasive means of following the patients with renovascular hypertension after angioplasty or surgical revascularization (Gruenweld et al, 1985; Geyskes et al, 1986; Gupta et al, 1985; Lamki et al, 1986; Probst et al, 1983). These studies clearly suggest that with successful balloon dilatation or surgical revascularization scintigraphic abnormalities are reversed. In treatment failures, abnormalities persist. Compared to angiography, radioisotope renography is less invasive and relatively safe and if the baseline test is abnormal, scintigraphy can be utilized to monitor the patients sequentially.

C. ULTRASOUND DOPPLER - A NEW TECHNIQUE FOR SCREENING OF RENOVASCULAR HYPERTENSION

Preliminary experience has shown that the ultrasound doppler characterization of renal blood flow pattern may be helpful to detect

renal artery obstruction (Jenni et al, 1986). Johann Doppler first described the effect that bears his name in 1842. He showed mathematically that the frequency of a traveling wave appears to increase to an observer who is moving towards its source and to decrease to an observer who is moving away from the source. To detect spatial velocity profiles of the renal arteries, one can use a real time scanner with pulsed Doppler System. The transducer is placed on the midline below xiphoid. By meticulous orientation of the transducer, a transverse scan can be obtained showing the abdominal aorta (in cross section) and the renal arteries (in long-axis). The Doppler beam should be selected such that it intersects the renal artery near the aorta. From the volume flow curve generated, the peak systolic value (S_1) and end systolic value (S_2) are obtained. The ratio S_2/S_1 is a measure of flow resistance. With proper application and interpretation of Doppler results, renal artery stenosis can be diagnosed or excluded (Jenni et al, 1986).

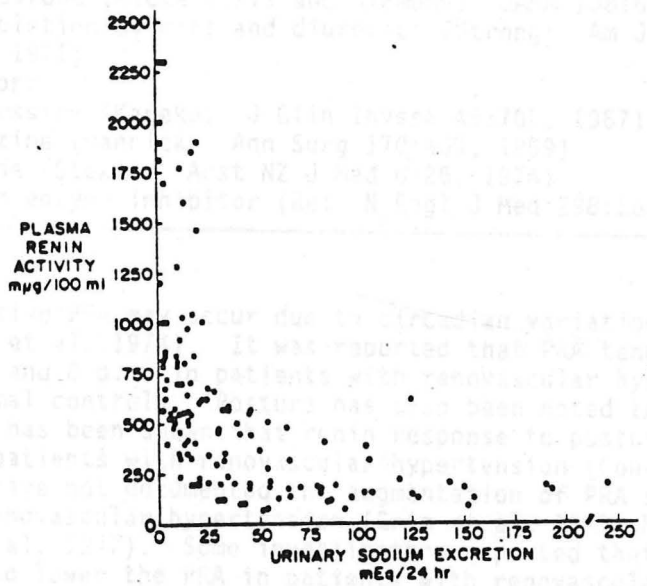
In the duplex system, the pulsed Doppler is interfaced with a real-time ultrasonic imaging system which then allows the source of the vascular signal to be visualized. Using this technique, Kohler and co-workers accurately evaluated the renal blood flow in 144 of 158 patients (90%) (Kohler et al, 1986). By applying the ratio of peak velocities in the renal artery and the aorta to distinguish stenotic from non-stenotic arteries, these workers achieved a sensitivity of 91% and a specificity of 95%. The precise sensitivity and specificity of ultrasound doppler in unselected population remains to be determined. It is too early to gauge its accuracy and predictive value although preliminary reports are encouraging.

D. PLASMA RENIN ACTIVITY (PRA)

Reliable measurement of PRA after the development of radioimmunoassay methodology provided another potential screening method to diagnose renovascular hypertension. As covered in the introduction, reduced perfusion pressure at the juxtaglomerular apparatus activates the renin release mechanism. Conceivably then the circulating level of angiotensin I (PRA) would be elevated in the presence of persistent ischemia to the kidney. Early studies (Kirkendall et al, 1967; Brown et al, 1966; Bath et al, 1968) suggested that measurement of peripheral plasma renin activity aided in the diagnosis of renovascular hypertension, but subsequent studies have shown that while a high peripheral PRA is suggestive, it is not diagnostic of the condition (Vaughan et al, 1973; Messerli et al, 1975; Salvetti et al, 1987; Tucker et al, 1978; Hansson et al, 1981). These studies demonstrate that 10-20% of patients with renovascular hypertension and with high PRA do not respond to renal revascularization. Conversely 5-40% of patients whose hypertension responded to revascularization had a low or normal PRA. Several studies concluded that while elevated PRA is suggestive of renovascular hypertension, a normal value does not exclude the diagnosis. It has been proposed, however, that since the peripheral PRA represents an index of renal renin secretion, it is valuable in the diagnosis of renovascular hypertension (Vaughan, 1985). Peripheral PRA obtained after 4 hours of ambulation when correlated with urinary excretion of sodium enhances its utility. Taken together, the analysis suggests that sensitivity and

specificity of elevated PRA in the diagnosis of renovascular hypertension are 57 percent and 66 percent, respectively. In these series, 71 percent of patients with a normal PRA benefited from surgery (Rudnick and Maxwell, 1984).

Figure 12 Relation of plasma renin activity to sodium excretion in patients with essential hypertension. ○ and □, low-renin hypertensives, some of whom increased their PRA on very restricted sodium intakes. ● and ■, normal-renin hypertensives. PRA was measured by bioassay. (From Jose A, Crout JR, Kaplan NM: *Ann Intern Med* 72:9, 1970.)



There are several reasons for the relative low specificity and sensitivity of PRA in the diagnosis of renovascular hypertension. Renin secretion is not constant and fluctuates widely (Morlin et al, 1982). PRA level is also influenced by sodium intake, posture (Davis, 1973), variety of antihypertensive drugs, age (Weidmann et al, 1978), sex, and race (Kaplan, 1976). While attempts have been made to interpret PRA with sodium balance (Brunner et al, 1972) (Figure 12), no control values can be obtained to account for all the factors affecting renin release. Even though the stenotic kidney may be secreting renin at an increased rate, the renin secretion from the contralateral kidney is suppressed. The net effect could result in a normal PRA (DeChamplin et al, 1965; Gross et al, 1965; Vaughan et al, 1973). While the interpretative weight of PRA is enhanced in relation to sodium excretion (Laragh et al, 1972), its sensitivity is not significantly changed even under such controlled circumstances (Rosenthal et al, 1981; Streeten et al, 1978; Vaughan et al, 1973). Segmental renal arterial lesions may not demonstrate an elevated peripheral PRA due to the dilutional effect of blood from the normal segments of the kidney (Schambelan et al, 1974). Expansion of volume that occurs in bilateral renal artery stenosis or in unilateral renovascular hypertension can reduce the PRA (Laragh et al, 1975). Several maneuvers have been used to stimulate PRA (Table 17) but the overall reliability of PRA by these techniques has not improved.

Table 17: Maneuvers to Augment Renin Release

Peripheral plasma renin activity
- Upright posture (Cohen: JAMA 197:143, 1966)
- Vasodilators (hydralazine) (Ueda: Arch Intern Med 122:387, 1968)
- Angiotensin blockade (saralasin or converting enzyme inhibitor) (Case: Ann Intern Med 91:153, 1979)

Renal vein renin ratio
- Upright posture (Mickelaskis and Simmons: JAMA 108:659, 1971)
- Sodium depletion by diet and diuretics (Strong: Am J Cardiol 27:602, 1971)
- Vasodilators
  - Nitroprusside (Kaneko: J Clin Invest 46:705, 1967)
  - Hydralazine (Mannick: Ann Surg 170:409, 1969)
  - Diazoxide (Stokes: Aust NZ J Med 6:26, 1976)
- Converting enzyme inhibitor (Re: N Engl J Med 298:582, 1978)

False negative PRA may occur due to circadian variation in renin secretion (Grim et al, 1974). It was reported that PRA tends to be higher at noon, 4 p.m. and 8 p.m. in patients with renovascular hypertension compared to normal controls. Posture has also been noted to affect the PRA values. It has been shown that renin response to posture is greatly exaggerated in patients with renovascular hypertension (Cohen et al, 1966). Others have not documented the augmentation of PRA sensitivity in patients with renovascular hypertension (Grim et al, 1979; Messerli et al, 1975; Melman et al, 1977). Some investigators reported that saline infusion fails to lower the PRA in patients with renovascular hypertension (Melman et al, 1977) but others found saline infusion unhelpful in diagnosing renovascular hypertension (Grim et al, 1979). In addition to these factors, other hypertensive disorders are associated with an elevated PRA such as malignant hypertension (Fitz and Armstrong, 1964), heart failure (Brown et al, 1970). Importantly, 15-20 percent of patients with essential hypertension have a high PRA (Laragh et al, 1972, Kaplan, 1977). A number of clinical conditions affect the renin levels (Table 18).

The process involved in establishing sodium balance, multiple physiological and pharmacological influences on PRA, variability in PRA assays, and the frequent impossibility of discontinuing antihypertensive medications make the peripheral PRA test an unreliable tool to screen patients for renovascular hypertension. Many commonly used drugs have been known to alter PRA (Table 19). Ideally, the PRA test should be performed when the patient is off all antihypertensive drugs but this is not possible in most instances.

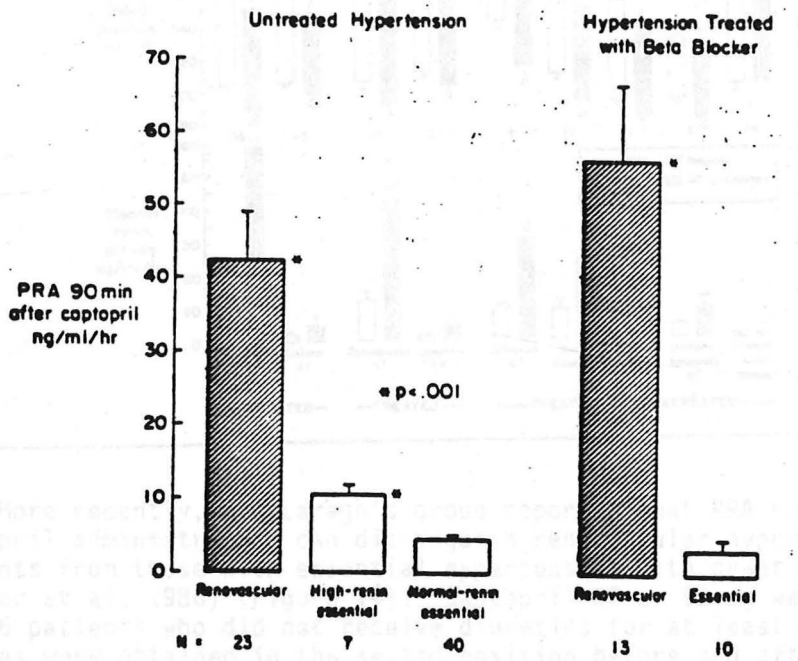
Table 18: Clinical Conditions Affecting Renin Levels

Decreased PRA	Increased PRA
Expanded fluid volume	*Shrunken fluid volume*
Salt loads, oral or IV	Salt deprivation
Primary salt retention (Liddle's syndrome, Gordon's syndrome)	Fluid losses
Mineralocorticoid excess	Diuretic-induced
Primary aldosteronism	GI losses
Congenital adrenal hyperplasia	Hemorrhage
Cushing's syndrome	Salt-wasting renal disease
Licorice excess	Decreased effective plasma volume
Deoxycorticosterone (DOC), 18-hydroxy-DOC excess	Upright posture
Catecholamine deficiency	Adrenal insufficiency
Autonomic dysfunction	Cirrhosis with ascites
Therapy with adrenergic neuronal blockers	Nephrotic syndrome
Therapy with β-adrenergic blockers	*Decreased renal perfusion pressure*
Hyperkalemia	Therapy with peripheral vasodilators
Decreased renin substrate (?)	Renovascular hypertension
Androgen therapy	Accelerated-malignant hypertension
Decrease of renal tissue	Chronic renal disease (renin-dependent)
Hyporeninemic hypoaldosteronism	Juxtaglomerular hyperplasia (Bartter's syndrome)
Chronic renal disease (volume-dependent)	*Catecholamine excess*
Anephric	Pheochromocytoma
Increasing age	Stress: hypoglycemia, trauma
Unknown	Exercise
Low renin essential hypertension	Hyperthyroidism
	Caffeine
	Hypokalemia
	Increased renin substrate
	Pregnancy
	Estrogen therapy
	Autonomous renin hypersecretion
	Renin-secreting tumors
	Acute damage to J-G cells
	Acute renal failure
	Acute glomerulonephritis
	Unknown
	High-renin essential hypertension

Table 19: Drug Effects on Plasma Renin Levels

Increase	Decrease
Antihypertensive drugs	
Diuretics	Reserpine
Mineralocorticoid antagonists (spironolactone)	Methyldopa
α-Blockers (e.g., dibenzyline)	Clonidine
Vasodilators (hydralazine, calcium-antagonists)	β-Blockers
Converting enzyme inhibitors (captopril)	
Saralasin	
Hormones	
Glucagon	Vasopressin
Estrogen	Somatostatin
Glucocorticoids	Mineralocorticoids
ACTH	
Drugs	
Anesthetics	Cardiac glycosides
Chlorpromazine	Lithium (small doses)
Caffeine	Phenobarbital
Theophylline	Inhibitors of prostaglandin synthesis
β-Agonists	(indomethacin, etc.)
Lithium (large doses)	

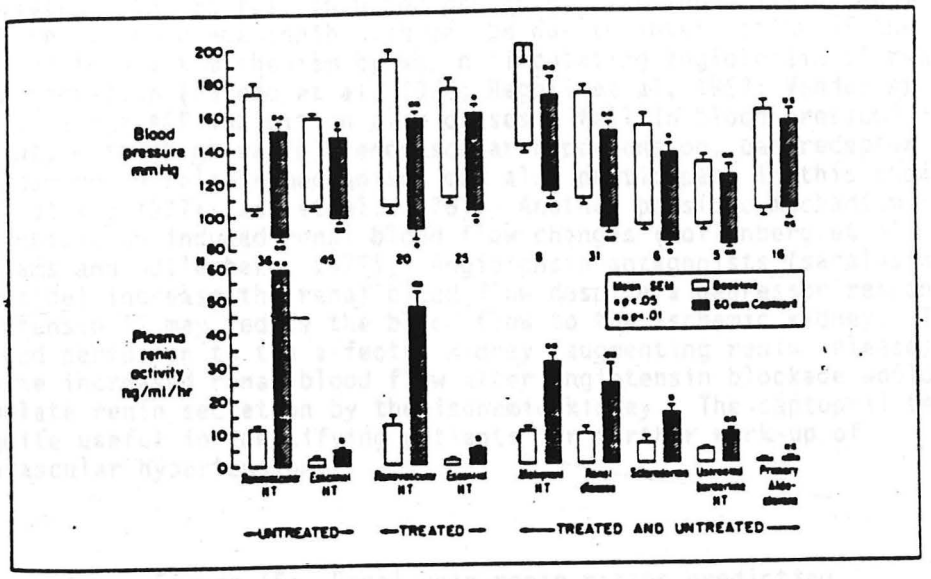
Figure 13: Levels of plasma renin activity in renovascular and essential hypertension 90 minutes after a single dose of captopril. A marked reactive hyperreninemia was found in the group with renovascular hypertension whether or not they were already receiving beta-blocker therapy. (From Case DB, et al: In: Laragh JH, et al, eds. Frontiers in Hypertension Research. New York: Springler-Verlag 1982a:541-50).



ENHANCING THE SENSITIVITY OF PRA WITH ANGIOTENSIN CONVERTING ENZYME INHIBITION:

Recently, ACE inhibitors were reported to enhance the sensitivity of peripheral PRA in the diagnosis of renovascular hypertension. ACE inhibition causes marked reactive hyperreninemia following angiotensin blockade with saralasin or teprotide (Case and Laragh, 1979) or with captopril (Muller et al, 1986; Imai et al, 1980). In patients with renovascular hypertension, captopril administration causes a significant increase in PRA (Figure 13). For example, Imai and co-workers noted that administration of 50 mg captopril caused a marked increase in peripheral PRA of patients with renovascular hypertension, whereas, the PRA response was not seen in patients with essential hypertension and in normotensive individuals.

Figure 14: Seated blood pressure and plasma renin response 60 minutes after an oral dose of captopril in groups of various types of treated and untreated hypertensive patients.



More recently, Dr. Laragh's group reported that PRA response to captopril administration can distinguish renovascular hypertension patients from those with essential hypertension with great precision (Muller et al, 1986) (Figure 14). Captopril 25 or 50 mg was administered to 246 patients who did not receive diuretics for at least 4 days. Blood samples were obtained in the seated position before and after captopril administration. At 60 minutes marked increase in PRA was noted in all 56 patients who proved to have unilateral renovascular hypertension. The criteria for captopril test that distinguished renovascular patients from those with essential hypertension are:

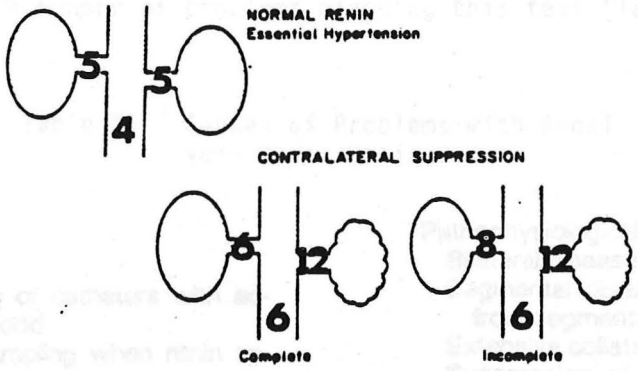
1) Stimulated PRA > 12 ng/ml/hour;
2) An absolute increase of PRA of 10 ng/ml/hour; and
3) A 150 percent increase in PRA or a 400 percent increase if the baseline PRA was under 3 ng/ml/hour.

Table 20: Method for Captopril Test
(From Muller FB et al: Am J Med 1986;80:633-44.

- The patient should maintain a normal salt intake and receive no diuretics
- If possible, all antihypertensive medications should be withdrawn three weeks prior to the test
- The patient should be seated for at least 30 minutes, and blood pressure measured at 20, 25, and 30 minutes (average the three readings for baseline); a venous blood sample is then drawn for measurement of baseline plasma renin activity
- Captopril (50 mg diluted in 10 ml of water immediately prior to the test) is administered orally
- Blood pressure is measured 15, 30, 40, 45, 50, 55, and 60 minutes after captopril; at 60 minutes, a venous blood sample is drawn for measurement of stimulated plasma renin activity

The sensitivity of the test was maintained even while the patients were taking non-diuretic antihypertensive drugs including beta-blockers. Its value was diminished in the presence of bilateral renal arterial disease, and renal insufficiency. The magnitude of PRA response correlated with the fall in blood pressure. The mechanism of augmented renin response to ACE inhibition may be due to interruption of the negative feedback mechanism by which circulating angiotensin II regulates renin secretion (Sancho et al, 1976; Regoli et al, 1962; Vander et al, 1967). Since ACE inhibition also causes a fall in blood pressure in patients with (high renin) renovascular hypertension, baroreceptor mediated renin release mechanisms may also participate in this phenomenon (Baer et al, 1977; Case et al, 1976). Another possible mechanism involves ACE inhibition induced renal blood flow changes (Hollenberg et al, 1976; Williams and Hollenberg, 1977). Angiotensin antagonists (saralasin, teprotide) increase the renal blood flow despite a depressor response. Angiotensin II may reduce the blood flow to the ischemic kidney. Thus, reduced perfusion to the affected kidney (augmenting renin release) despite increased renal blood flow after angiotensin blockade would stimulate renin secretion by the ischemic kidney. The captopril test may be quite useful in identifying patients for further work-up of renovascular hypertension.

Figure 15: Renal vein renin ratios predicting renovascular hypertension



E. RENAL VEIN RENINS

It has been observed that in patients with renovascular hypertension, the renin output from the stenotic side was higher compared to the contralateral side (Judson and Helmer, 1965; Judson and Helmer, 1960; Helmer, 1964; Tremblay et al, 1964; Vaughan, 1985; Vaughan et al, 1981). The most accepted approach has been calculation of renal vein renin ratio, that is, stenotic side divided by contralateral-side PRA. A major limitation is in selecting a "positive" ratio that would identify

patients with remediable "functional" renal artery stenosis. Traits of renin dependent unilateral renovascular hypertension are:

1) Increased renin secretion from the affected side
2) Suppression of contralateral renin release

Vaughan et al have added a third criterion based on their analysis of renal vein and renal arterial renin relationships in patients with hypertension. These workers calculated that the mean renal venous renin is about 25% higher than the arterial renin. Thus, a total renin increment of approximately 50% is necessary to maintain a given PRA. The degree to which the increment exceeds 50% becomes an index of renal ischemia. While Vaughan et al used all the criteria to identify and treat patients with renovascular hypertension, a simple renal vein ratio of stenotic: non-stenotic side has been applied in most centers.

In their initial report, Judson and Helmer used a renal vein renin ratio of 2 or greater as a predictor of surgical cure of renovascular hypertension. For some years now, the renal vein renin ratio has been a widely accepted criterion to diagnose "functional" renovascular hypertension. One reason for the widespread acceptance of renal vein renin ratio is that the absolute peripheral PRA was not sensitive and the ratio was not altered by factors that ordinarily affected the total peripheral PRA. It has been claimed that measurement of the renal vein renin ratio may be the best single method for predicting the response to surgery (Brown et al, 1979). In considering the value of renal vein renin determinations in the diagnosis of renovascular hypertension, one should be cognizant of a number of problems plaguing this test (Table 21 and Figure 16).

Table 21: Causes of Problems with Renal Vein Renin Ratios

False-negatives
- Errors of technique
  - Improper positioning of catheters with admixture of caval blood
  - Nonsimultaneous sampling when renin secretion is changing
  - Interference by contrast media
  - Diuretic-induced increase in renin from nonstenotic kidney without increase from stenotic kidney
  - Multiple renal veins (found in 25% on right, 2% on left)
  - Errors in radioimmunoassay, particularly when renin levels are low
  - Use of excessively high value for division between normal and abnormal
- Pathophysiological problems
  - Bilateral disease of near equal degree
  - Segmental disease (and failure to sample from segmental vein)
  - Extensive collateral circulation
  - Suppression of renin secretion by volume expansion, adrenergic blocking drugs, etc.

False-positives
- Nonsimultaneous sampling when renin secretion is changing
- Interference by contrast media
- Errors in radioimmunosassay, particularly when renin levels are low
- Asymmetric nephrosclerosis
- Inadequate surgical repair
- Use of excessively low value for division between normal and abnormal
- Coexisting primary (essential) hypertension

Figure 16: Diagram depecting possible causes of misleading renal vein renin determinations. The primary source of error has been in false negative test results.

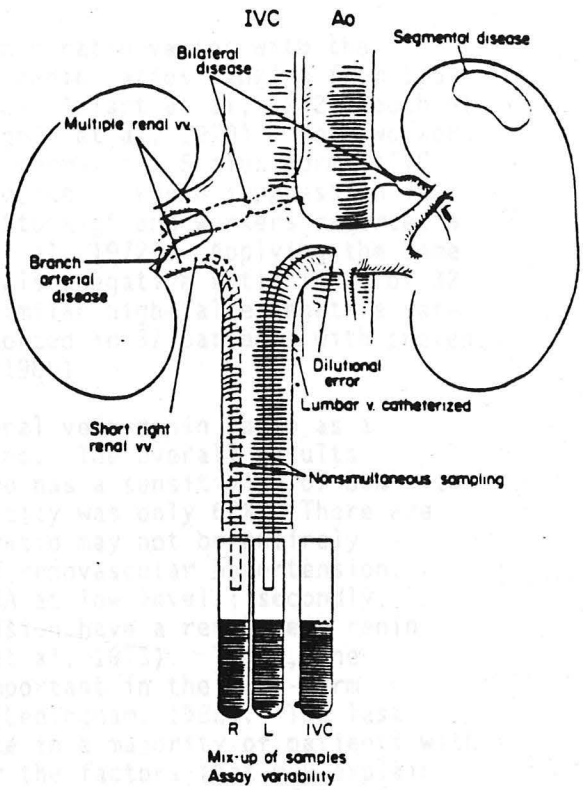


Table 22: Operative Results versus Renal Vein Renin Ratios (RVRR) in Patients with Unilateral or Bilateral Renovascular Hypertension.

	Sensitivity RVRR+/Disease+	Specificity RVRR−/Disease−	Surgical Improvement	
			Improved/RVRR−	Improved/RVRR+
All 58 series	875/1097 (80%)	120/193 (62%)	222/342 (65%)	875/948 (92%)
Bilateral RVHT (10 series)	61/89 (68%)	10/15 (67%)	28/38 (74%)	61–66 (92%)
Unilateral RVHT stimulated (16 series)	300/377 (80%)	24/45 (53%)	77/101 (77%)	300/321 (93%)
Simultaneous sampling (10 series)	207/258 (80%)	19/30 (63%)	51/70 (73%)	207/218 (95%)

• Data from Rudnick MR, Maxwell MH: In Narins RG (ed): *Controversies in Nephrology and Hypertension*, New York, Churchill Livingston, 1984, pp 128–129.

The predictive value of renal vein renin ratio varies with the definition of a positive test. Renal vein renin ratios ranging from 1.5 to 2.5 have been applied (Mackay et al, 1983; Arlart et al, 1982; Couch et al, 1976; Marks and Maxwell, 1975; Bourgoignie et al, 1970). Some workers have defined a positive test as abnormal: normal > 1.5 plus normal/IVC ratio < 1.3, the latter being taken as evidence of renin suppression in the normal kidney. Using these criteria, Stockigt and Workers reported a false positive rate of only 6% (Stockigt et al, 1972). Applying the same criteria, Maxwell and colleagues found a false negative ratio in 23 of 32 patients (72%) (Maxwell et al, 1977). A similar high false negative rate of renal vein renin ratio was recently reported in 37 patients with proven renovascular hypertension (Sellars et al, 1985).

Table 22 summarizes the utility of renal vein renin ratio as a diagnostic test in renovascular hypertension. The overall results demonstrate that the renal vein renin ratio has a sensitivity of 80% with a false negative rate of 20%. The specificity was only 62%. There are several reasons why the renal vein renin ratio may not be entirely reliable in the diagnosis and treatment of renovascular hypertension. First, the imprecision of RIA to detect PRA at low levels; secondly, 13-19% of patients with essential hypertension have a renal vein renin ratio > 1.5 (Maxwell et al, 1975; Sealey et al, 1973). Third, the evidence that hyperreninemia may not be important in the long-term maintenance of renovascular hypertension (Ledingham, 1982). The last factor certainly is of paramount importance in a majority of patients with renal artery stenosis. I want to consider the factors that may explain the occurrence of a significant number of false positive and false negative renal vein renin ratio tests.

- Bilateral Renal Artery Stenosis

The hypertension in patients with bilateral renal artery stenosis is analogous to the one-kidney Goldblatt hypertension (Laragh et al, 1975) i.e. it may be volume dependent hypertension. In the Co-operative Study, 25% of patients with renovascular hypertension had bilateral renal arterial lesions. Thus, the renal vein renin ratio is unlikely to be of any help although the kidney with higher renin output may play a pathogenetic role. It is not surprising that in a number of series, renal vein renin ratio was unhelpful in the diagnosis of patients with bilateral renal artery stenosis (Bath et al, 1968; Bourgoignie et al, 1970; Dean et al, 1966; Gittes and McLaughlin, 1974; Klatte et al, 1971; Poutasse et al, 1973; Rosenthal et al, 1981; Stockigt et al, 1973; Strong et al, 1971). In these studies, the renal vein renin ratio showed a false negative rate of 32%, which is much higher than obtained in unilateral renal artery stenosis. Furthermore, many patients without lateralizing renal vein renin ratio benefited from surgical revascularization of one or both renal artery lesions. These data then would suggest that many patients with bilateral renal artery stenosis share the same pathophysiologic mechanism as patients with unilateral renal artery stenosis. Despite the morphologic evidence of bilateral RAS, in many patients only one lesion is functionally operative (Klatte et al, 1971).

Obviously, in patients with bilateral renal artery stenosis with lateralizing renal vein renin ratio, revascularization or angioplasty should be performed on the lateralizing side first. In patients without

lateralization of renal vein renin ratio, the side with greater stenosis should be considered for operative treatment or angioplasty (Dean et al, 1966; Strong et al, 1971).

- Segmental Renal Arterial Lesions

Segmental ischemic lesions due to branch stenosis, focal infarction, and segmental hypoplasia may result in a false negative renal vein renin ratio. It has been estimated that segmental lesions occur in 13% of patients with renovascular hypertension (Bookstein et al, 1972). When segmental renal occlusive lesions are present, blood draining the segmental area may be diluted by venous blood from the remainder of the kidney with the net result that renin in the main renal vein may not be high. When the renin sampling is performed in the venous effluent from the segmental veins, and compared to the contralateral renal vein, the ratio becomes meaningful (Schambelan et al, 1974). Therefore, segmental renal vein renin should be measured in patients with segmental renal arterial lesions.

- Dilutional Errors

Improper placement of the catheter may cause admixture of renal venous blood with blood from non-renal sources, thus diluting the renin concentration and falsely lowering the renin ratio (Guedon et al, 1972; Ofstad and Willassen, 1977; Winer et al, 1967). This error is particularly likely to occur with the right renal vein because of its short length. Too vigorous aspiration of the blood may cause an admixture with vena caval blood. The presence of multiple renal veins may also give rise to a false renal vein renin ratio if the blood is drawn from the vein draining the non-ischemic zones (Pawsey et al, 1971; Poutasse et al, 1973). A falsely negative renal vein renin ratio could occur if the renin sampling is done while the patient strains, Valsalva maneuver causes hemodilution which could decrease the renin concentration (Ofstad and Willassen, 1977).

- Nonsimultaneous Sampling of Renin

Since renin secretion may fluctuate spontaneously and rapidly, it has been suggested that nonsimultaneous sampling of the renal vein renins may cause a false positive or a false negative ratio (Poutasse et al, 1973). Although simultaneous sampling is desirable, Whelton et al did not find any difference between simultaneous and nonsimultaneous sampling (Whelton et al, 1977).

- Interfering Substances

False negative renal vein renin ratio may result from the use of contrast media (Winer et al, 1967). However, when the subjects were carefully prepared, contrast had no bearing on the renal vein renin value (Whelton et al, 1977). High concentrations of heparin (in the collection tubes) has been shown to interfere with renin assays (Kaufman et al, 1970; Kaneko et al, 1967). Lower concentrations (< 40 U/ml) of heparin probably do not interfere with renin assays.

- Non-renin Mediated Renovascular Hypertension

Marks and colleagues described two patients with renal artery stenosis who demonstrated low PRA, and non-lateralizing renal vein renin ratio whose hypertension was cured by surgical revascularization (Marks et al, 1977). The possibility of factors other than renin in the pathogenesis of renovascular hypertension can not be ignored (Macdonald et al, 1970; Macdonald et al, 1975).

STIMULATORY MANEUVERS TO INCREASE THE SENSITIVITY OF RENAL VEIN RENIN RATIO.

Since the basal renin vein ratios have yielded inconsistent results, several stimulatory maneuvers have been used to facilitate the sensitivity of renin measurements and to maximize the lateralization of renin secretion. The premise for these stimulatory maneuvers is that the renin secretion from the stenotic kidney is of greater magnitude than the contralateral (normal) kidney (Kaneko et al, 1967; Ueda et al, 1968). Therefore, for a given stimulus there will be a greater output of renin from the ischemic kidney compared to a normal kidney. The inability of a stimulus to increase the renin secretion from the contralateral (normal) kidney to the same magnitude as the stenotic kidney accentuates the disparity between the renal vein renin levels, thus raising the ratio (Huvos et al, 1965; Kaneko et al, 1967; Marks and Maxwell, 1975; Poutasse et al, 1973; Ueda et al, 1968). The renin content in the opposite kidney is reduced in unilateral renovascular hypertension (Gross and Lichtlen, 1958; Hass and Goldblatt, 1963). Thus, the contralateral kidney fails to mount the same increase in renin as the ischemic side. Additionally, high circulating levels of angiotensin II cause inhibition of renin secretion from the normal kidney (DeChamplain et al, 1966; Vander and Geelhoed, 1965). The use of stimulatory maneuvers would thus promote the sensitivity of renal vein renin ratio.

- Sodium Depletion

Negative sodium balance achieved either by diuretics or salt restriction increases renin secretion in general (Cohen et al, 1967; Gordon et al, 1966; Weinberger et al, 1968). Similar maneuvers in patients with renovascular hypertension increase the sensitivity of renal vein renin ratio (Hunt et al, 1969; Lüscher et al, 1981; Strong et al, 1971; Vermillion et al, 1969; Aurell et al, 1981). The administration of furosemide 40mg-80mg by oral or intravenous route has been shown to increase the renal vein renin ratio in several studies but some have noted that furosemide does not increase the predictive value of renal vein renin measurements (Chuang et al, 1979; Whelton et al, 1976).

- Upright Posture

It has been shown by many investigators that upright posture (20-30 minutes) reduces the incidence of false negative renal vein renin results (Aurell et al, 1981; Cohen et al, 1966; Grim et al, 1974; Melman et al, 1977; Michelakis and Simmons, 1969; Michelakis et al, 1969). A disparity in the renin secretion from the two sides is exaggerated by upright posture which can be achieved with tilting during the collection of renal venous blood.

PHARMACOLOGIC AGENTS

A variety of pharmacologic agents have been used to increase the value of renal vein renin ratio (Thind, 1985; Rudnick and Maxwell, 1984). Intravenous hydralazine has been reported to enhance the renin secretion from stenotic kidney (Huvos et al, 1965; Kirkendall and Kioschus, 1970; Mannick et al, 1969; Sinako and Mirkin, 1982; Thind et al, 1984). Possible mechanisms for hydralazine induced renin release include systemic reduction in blood pressure, alteration of renal hemodynamics, and activation of sympathetic neural mechanisms. Other direct arterial dilators such as nitroprusside and diazoxide have also been shown to improve the reliability of renal vein renin ratio (Stokes et al, 1976; Kaneko et al, 1967).

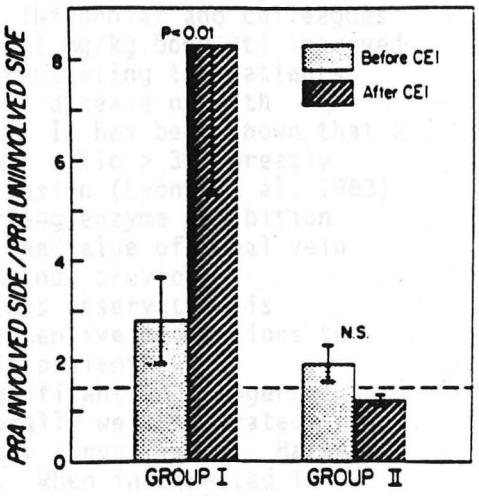


Figure 17: Mean (±SE) renal vein plasma renin activity (PRA) ratio before and after the CEI SQ 20881 in seven patients with unilateral renovascular disease (Group 1) and seven patients without renovascular disease (Group II). (From Re R et al: N Engl J Med 1978;298:582).

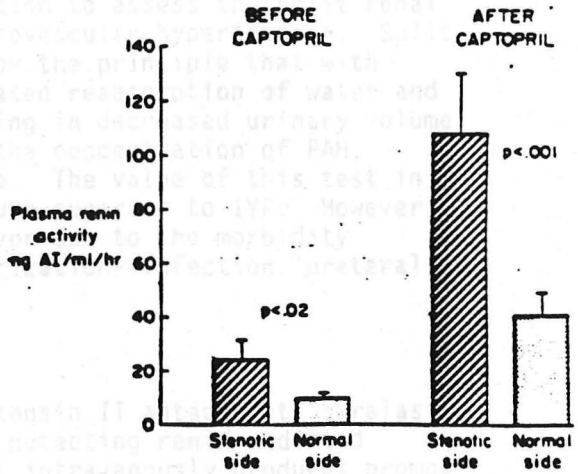


Figure 18: Renal vein renin determinations (renal vein levels only) in patients with documented renovascular hypertension before and after captopril stimulation. Captopril accentuates renin secretion from the ischemic kidney. Not shown are the inferior vena cava levels which are the same as the levels from the normal size both before and after captopril stimulation. (From Vaughan ED Jr et al: In: Kaplan NM et al, eds. The Kidney in Hypertension. New York: Raven Press 1987:91-108).

Converting enzyme inhibitors have been used to improve the sensitivity of the renal vein renin ratio in the diagnosis of renovascular hypertension. PRA rises after angiotensin blockade with saralasin (Case et al, 1976; Baer et al, 1977; Case et al, 1979), teprotide (Case et al, 1977; Re et al, 1978), and captopril (Bravo et al, 1979; Case et al, 1978; McGregor et al, 1979; Case et al, 1979) (Figures 17 and 18). Although the rise in PRA could be a consequence of baroreceptor stimulation of renin release, the most attractive explanation is a fall in angiotensin II and interruption of the negative feedback mechanism on renin release. Inhibition of angiotensin II formation causes marked reactive hyperreninemia in patients with renovascular hypertension. Re et al showed in 14 patients with unilateral renal artery stenosis, a parenterally active converting enzyme inhibitor improved the diagnostic accuracy of renal vein renin ratio. Similarly, Thibonnier and colleagues have demonstrated that captopril administration (1 mg/kg body wt) improved the accuracy of renal vein renin ratio by differentiating the patients with unilateral lesions from those with bilateral disease or with essential hypertension (Thibonnier et al, 1984). It has been shown that a 30 minute post captopril (25 mg) renal vein renin ratio > 3.0 greatly enhances the probability of renovascular hypertension (Lyons et al, 1983). Renal vein renin determination following converting enzyme inhibition offers several advantages. First, it improves the value of renal vein renin ratio, second, there is no need to discontinue previous antihypertensive drugs except the diuretics. This observation is pertinent since discontinuation of all antihypertensive medications to permit renin measurements may not be possible in patients with renovascular hypertension who often exhibit significant and dangerous elevation in blood pressure. Third, it is generally well tolerated. Patients with bilateral renal lesions need closer surveillance. Marked hypotension can be reversed by saline infusion. When interpreted in concert with clinical and radiologic findings, post-captopril renal vein renin measurements enhance the diagnostic precision.

SPLIT FUNCTION TESTS

In most centers, ureteral catheterization to assess the split renal function are no longer used to diagnose renovascular hypertension. Split function studies were originally proposed on the principle that with decreased renal blood flow, there is increased reabsorption of water and sodium from the glomerular filtrate resulting in decreased urinary volume and sodium with corresponding increase in the concentration of PAH, insulin and creatinine on the affected side. The value of this test in predicting surgical cure approaches 75%, much superior to IVP. However, these tests have fallen into general disfavor due to the morbidity associated with bilateral ureteral catheterization--infection, ureteral obstruction and sometimes renal shutdown.

SARALASIN TEST

A vasodepressor response to the angiotensin II antagonist, saralasin, has been proposed as a diagnostic test for detecting renin-mediated hypertension. Administration of this agent intravenously produces prompt blood pressure reduction in patients with "angiotensinogenic" hypertension by blocking the action of endogenous angiotensin II at the vascular

receptor level. In order to enhance its specificity, the test is performed with the subject in a sate of mild sodium depletion (net sodium loss of 100-200 mEq Na). This is accomplished by a low salt diet and prior administration of a diuretic, usually furosemide. In a volume-replete subject, saralasin may exert an agonistic response resulting in elevated blood pressure.

The initial studies utilizing this procedure for the diagnosis of renovascular hypertension reported encouraging results. But subsequent studies revealed a high rate of false responses. The saralasin test quickly fell into disfavor and it is no longer marketed.

X. ANATOMIC DIAGNOSIS OF RENAL ARTERY STENOSIS

Renal arteriography is the gold standard for diagnosing renal artery stenosis. While the conventional arteriography remains the most accurate way of detecting renal artery stenosis, in the last few years, digital subtraction angiography (DSA) has been made available for this purpose. Since DSA has been extensively utilized, I will cover this technique first and in some detail.

Table 23: Definitive Studies

1. Conventional Arteriography
2. Digital Angiography
3. Renal Vein Renin Ratio

A. DIGITAL SUBTRACTION ANGIOGRAPHY

DSA is one of the notable advances in radiologic techniques in recent years. DSA techniques culminated from the union of radiographic subtraction methods of yesteryear and today's computer assisted video-imaging process. Basically DSA consists of obtaining a baseline image without contrast, i.e. the mask, storing it in a computer, obtaining another image of the structure with contrast and comparing it with the mask. Subtracting the mask eliminates bone and soft tissue views leaving only the blood vessels on the final image. Computer processing of mask and contrast image allows demarcation between the vascular and non-vascular structures. Digital processing of information makes it possible to manipulate and select data before or after the images are recorded. It also allows preservation and rapid retrieval of a large body of information eliminating cumbersome storage systems. The field of interest - renal vasculature may be defined by area detection or line - scanned systems. Area detection systems image the field of interest at the same time. Line-scanned systems compose an image by rapidly exposing single lines such as that produced on a television screen. Area detector systems show good spatial resolution. Line-scanned systems require less contrast medium and larger fields can be imaged. The image acquisition system consists of a specially designed X-ray image intensifier and

television video coupled to an image processor, where images are recorded, manipulated, and displayed on a CRT. Typically, images are obtained at a rate of 1-2 per second before and after the injection of contrast material. The images are converted into a digital format and stored on a digital disk. As mentioned earlier, images obtained before the contrast injection are subtracted from images obtained after contrast administration such that the final image is that of iodine-contained arterial structures. The main difference between a digital angiographic system and a computer tomography (CT) system is that the X-ray recording medium in digital systems is an intensifier - TV camera system producing planar images whereas a circular array of photodiodes in CT imaging produces a cross-sectional image. Having covered the principles of DSA, let's turn to the application of this technique in the morphologic delineation of renal artery stenosis.

INTRAVENOUS DSA (IV-DSA)

IV DSA has been extensively used in the diagnosis of renovascular disease (Hillman, 1985; Hillman, 1987 [From Kaplan NM, Brenner BM, Laragh JH, eds. Perspectives in Hypertension, Volume 1: The Kidney in Hypertension. New York: Raven Press, 1987.]; Gomes et al, 1983; Chang et al, 1984; Smith et al, 1982). Renal IV-DSA is performed by injecting 40-50ml contrast material via the catheter placed in antecubital vein or in the right atrium. Most centers prefer central catheterization over the antecubital injection because of better technical results. During the imaging, the patient is instructed to stay motionless. Central catheterization, the use of a pigtail catheter with multiple sideholes, and rapid bolus injection maximize the outcome of the procedure (Hillman, 1985).

Although IV-DSA has been introduced and utilized as a safe, relatively inexpensive, and convenient procedure to document renal arterial lesions, more recent experience suggests that its sensitivity may not be as high as originally proposed (Randall et al, 1983; Buonocore et al, 1981). In the experienced hands, its sensitivity approaches 90% (Hillman, 1985) but this is probably an exaggerated figure (Harvey et al, 1985; Fiedler and Peters, 1985). The reliability of IV-DSA has been seriously questioned (Vinocur, 1984). Proponents of IV-DSA counter that the technique is a victim of misguided use and inflated claims and it has been argued that in cooperative patients, IV-DSA may still be applicable (Hillman, 1987). Patients with low cardiac output will likely show a poor study as do patients who can not stay still during the procedure. The lower spatial resolution in combination with low contrast concentrations makes it difficult to visualize small lesions.

Figure 19: The IV-DSA study depicts a lengthy atherosclerotic stenosis of the left renal artery (arrow).

The main advantages of IV-DSA compared to conventional arteriography are convenience, less cost, and less risk to the patient. While IV-DSA can identify atherosclerotic lesions, its sensitivity in identifying fibromuscular dysplasia is uncertain. Moreover, the distal arterial anatomy is poorly visualized with IV-DSA. When compared with conventional arteriography, certain disadvantageous differences come to mind. First, the technique is susceptible to motion artifacts and requires full cooperation of the patient. Second, it has a decreased spatial resolution that limits the imaging of distal vasculature. This is particularly disadvantageous in patients with fibromuscular dysplasia in whom the renal artery stenosis is characterized by distal lesions. Third, the IV-DSA images sometimes are non-interpretable, especially in obese patients and in those with cardiac decompensation.

Table 24: Disadvantages of intravenous renal digital subtraction angiography

Low spatial resolution
Small field size
Increased irradiation dose
Nonselective contrat injection
High contrast load

A recent detailed analysis of various screening procedures suggests that the value of IV-DSA may have been overemphasized (Table 25).

Table 25: Sensitivity and Specificity of Screening Tests for Renovascular Hypertension (Modified From Havey et al, 1985)

	No. Patients with RAS	No. Patients Without RAS	Sensitivity %	Specificity %
IVP	2040	2133	74.5	86.2
RENOGRAM	934	951	74.4	77
DSA	# DSAS 1218	#Angio 242	87.6	89.5

Table 26: Predictive value of screening tests for renovascular hypertension* (From Vaughan et al, 1987)

	IVP[b]	DIVA[b]	PRA[c,d]	Single dose[e] captopril
Sensitivity (%)	75	88	80	100
Specificity (%)	86	89	84	95
False + (%)	14	11	16	5
False - (%)	25	12	20	0
Predictive value (%)				
Prevalence 2%	9.9	14.6	9.3	29
5%	22.1	30.5	20.8	51.3
10%	37.5	48.1	35.7	69
Exclusion value (%)				
Prevalence 2%	99.4	99.7	99.5	100
5%	98.5	99.3	98.8	100
10%	96.7	98.5	97.4	100

Calculations:

$$\text{Predictive value} = \frac{\text{Sensitivity X prevalence}}{\text{(Sens. X prev.) + false pos. rate X (100 - prev.}} \text{ X } 100$$

$$\text{Exclusion value} = \frac{\text{Specificity X 100 - prevalence)}}{\text{[Specif. X (100 - prev.) + fase neg. rate] X prev.}} \text{ X } 100$$

*Abbreviations: (IVP) intravenous urogram; (DIVA) digital angiography; (PRA) plasma renin activity.
b = Harvey et al, 1985
c = Pickering et al, 1984b
d = Brunner et al, 1973
e = Muller et al, 1986

INTRA-ARTERIAL DSA (IA-DSA)

Advancements in the digital technology have led to the use of IA-DSA in the diagnosis of renal arterial lesions. A number of qualities inherent in IA-DSA make it considerably superior to IV-DSA. Arterial catheterization from a femoral approach is followed by injection of low-dose intra-arterial delivery of the contrast at the appropriate region (origin of renals). The main differences from conventional arteriography are the smaller size catheter use and generally smaller amount of dye required to obtain satisfactory images. Of course, the examination time is shortened. Renal arteriography using the IA-DSA technique can be performed with 20% of the contrast material required for IV-DSA and 12% of that required for conventional arteriography (Kaufman et al, 1984). The reduced contrast dose is especially advantageous in patients who are at an increased risk of dye-induced renal injury. Another advantage of IA-DSA over conventional arteriography is the reduction in patient discomfort

because of the use of dilute contrast material. In contrast to conventional arteriography, in IA-DSA the waiting time for obtaining scout films and for film processing is eliminated. The ability to reduce the catheter size and arterial catheter time should reduce the complications from arterial procedures (Hawkins, 1972). In view of these advantages, IA-DSA has been applied to diagnose renal arterial lesions (Kaufman et al, 1984; Crummy et al, 1982; Davis and Hoffman, 1983). The diagnostic accuracy of this technique closely approaches the results from conventional arteriography. The trends clearly suggest that IA-DSA will become the preferred approach to diagnose renal artery disease.

There are certain disadvantages inherent in IA-DSA. The images although superior to those obtained from IV-DSA still have less spatial resolution than conventional radiographic film techniques. Thus fine details of entire renal vascular architecture can not be obtained. The complications of arterial puncture - hemorrhage, thrombosis, embolization - can occur although rarely.

The predictive values of various screening procedures are shown in Table 26.

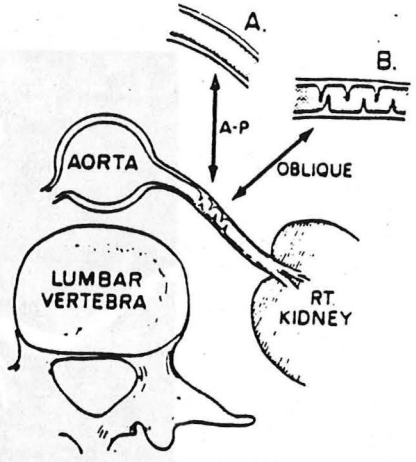


Figure 20: Graph illustrating how the septa of fibromuscular dysplasia can be missed. A, when the vessel is viewed with an AP arteriogram, the septa are masked by the overlying dye column. B, they are demonstrated by oblique projection, placing the vessel in a perpendicular direction and the septa parallel to the direction of the x-ray. (From Dean RH: Renovascular Hypertension. In: Moore WS, ed. Vascular Surgery: A comprehensive Review. New York: Grune and Stratton, 1983:433-65.

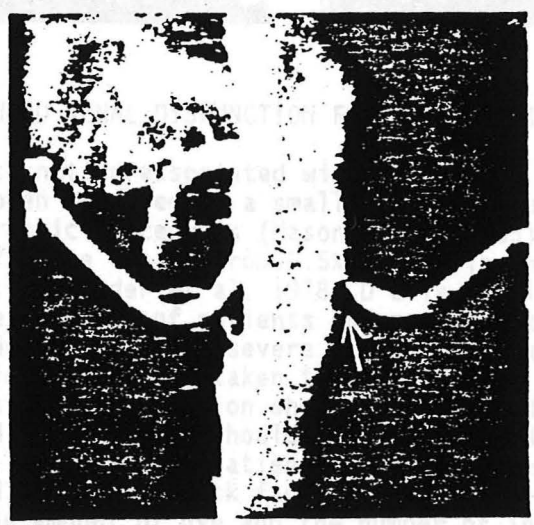
B. CONVENTIONAL RENAL ARTERIOGRAPHY

Although the need for conventional renal arteriograms for diagnosis of renal artery stenosis has decreased after the advent of DSA, it is the only procedure that yields complete information of the renal vascular architecture and about the collateral blood vessels. Renal angiography is recommended when DSA facilities are not available or when DSA provides suboptimal images. Even in the best hands 13% of patients initially evaluated with DSA require renal arteriography for better definition of renal arteries (Hillman, 1983). Some authors, citing their earlier experience, concluded that arteriography is the most definitive and appropriate procedure to diagnose renal artery lesions (Bookstein et al, 1975; Stenfanini et al, 1978; Lalli, 1981; Bookstein et al, 1972).

The preferred approach involves percutaneous femoral artery puncture and catheterization of the abdominal aorta by Seldinger technique. Aortography is first performed to define the origin and number of renal arteries. Selective catheterization of renal vessels is performed next to further study the stenosis and collateral circulation. In addition to anteroposterior projection, oblique views should be obtained especially of the origin of right renal artery (Figure 20).

The primary goal of arteriography is to ascertain definitively whether renal artery stenosis is present and if it is found, the location and severity should be defined to plan proper therapy. A 50% reduction in luminal diameter represents an approximate 80% decrease in the area of vessel lumen. Some believe that this represents critical narrowing and greater degrees of stenosis result in progressive reduction of renal blood flow (Anderson, 1979; Bookstein et al, 1972; Kaufman, 1979; May et al, 1963). Others, however, provided a contrary viewpoint that there is a poor correlation between the degree of stenosis and renal blood flow (Cho, 1982; Ernst et al, 1972). The importance of the length and number of stenoses is not clear. The arteriographic appearance of atherosclerotic lesions and fibromuscular dysplasia are shown in Figures 21 and 22.

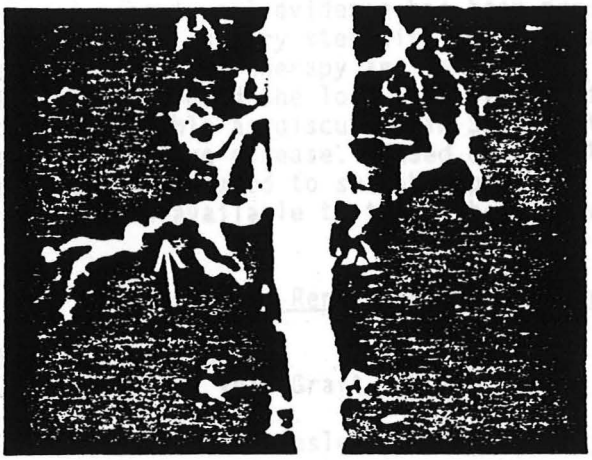
Figure 21: Typical atherosclerotic renal artery stenosis in the proximal portion of the main renal artery.



The presence of collateral circulation has been cited as a radiographic sign of significant renal artery stenosis (Bookstein et al, 1975; Bookstein, 1966; Cho, 1982). While the presence of collaterals indicates significant impairment of renal blood flow, their absence should not imply that a stenosis is not important. When collaterals are not easily apparent, pharmacoangiography has been advocated to facilitate their appearance (Bookstein et al, 1975; Bookstein, 1966; Bookstein and Ernst, 1973). For this purpose, Bookstein has advocated the use of acetylcholine, epinephrine or both. Acetylcholine produces parenchymal vasodilation in all but severe cases of nephrosclerosis causing the reversal of exorenal flow. It has not been demonstrated that the

demonstration of collaterals enhances the discriminatory power of renal arteriogram. Limited experience with out-patient conventional angiography indicates that the procedure can be safely performed in the out-patient setting with a 4-6 hour surveillance (Saint-Georges and Aube, 1985; Adams and Roub, 1984).

Figure 22: Typical fibromuscular dysplasia with "string of beads" appearance.



CONTRAST MEDIUM INDUCED RENAL DYSFUNCTION FOLLOWING ANGIOGRAPHY

Acute renal dysfunction associated with the use of radiographic contrast media has been observed in a small percentage of patients undergoing arteriographic procedures (Mason et al, 1985). The reported incidence of renal failure ranges from 0.5% to 38% in the high-risk groups (Swartz et al, 1978; Alexander et al, 1978; D'elia et al, 1982; Krumlovsky et al, 1978). Since a number of patients undergoing evaluation for renovascular hypertension may have severe vascular disease or renal impairment, precautions should be taken to minimize the dye induced complications. First, renal function should be assessed prior to angiography. Second, the patient should not be volume depleted before and after the procedure. In selected patients, hydration should be supplemented. Third, the known risk factors, e.g. diabetes, should be defined. Fourth, the amount of dye and the number of injections should be kept to a minimum, especially in patients with azotemia. Contrast medium doses containing less than 80g of iodine rarely cause renal dysfunction (Lang et al, 1981). Fifth, if a patient has demonstrated dye induced renal dysfunction, additional studies should be avoided or postponed. With these precautions, the hazards of angiography on renal function can be greatly minimized (Kumar et al, 1981).

XI. MANAGEMENT OF RENOVASCULAR HYPERTENSION

The optimal method of treating patients with renovascular hypertension remains an elusive goal. What constitutes appropriate management - medical, surgical, angioplasty - is a matter of ongoing

debate. Each therapeutic modality has its advocates, advantages, and disadvantages. A number of factors should be considered in determining the choice of therapy in a given patient. These include the functional correlates of renal artery stenosis, general medical condition of the patient, natural history of the renal arterial disease, renal function, response to medical treatment, and importantly, the expertise to perform surgical revascularization or percutaneous transluminal angioplasty (PTA). If medical therapy is chosen, it should be done with the knowledge that it can only control hypertension without an effect on renal ischemia. Over the last several years, unequivocal evidence has been presented that a functionally significant renal artery stenosis should be repaired. The long-term consequences of medical therapy are inferior to surgical therapy. Uncertainty looms around the long-term results from PTA. Sufficient evidence is available as discussed in Section VII that renal artery stenosis is a progressive disease. Based on this knowledge, PTA or surgical treatment should be offered to suitable patients although effective medical therapy is available to treat their hypertension.

Table 27: Management of Renovascular Hypertension

1. Drug Therapy
2. Surgical - Vein Graft, Dacron Graft, Nephrectomy, Etc.
3. Percutaneous Transluminal Angioplasty

A. SURGICAL THERAPY

--------It may come about that from the smoke and noise of the battle...the urologist will emerge the hero when he proclaims "Well, I once had a case...and I took one kidney out...and I cured high blood pressure."

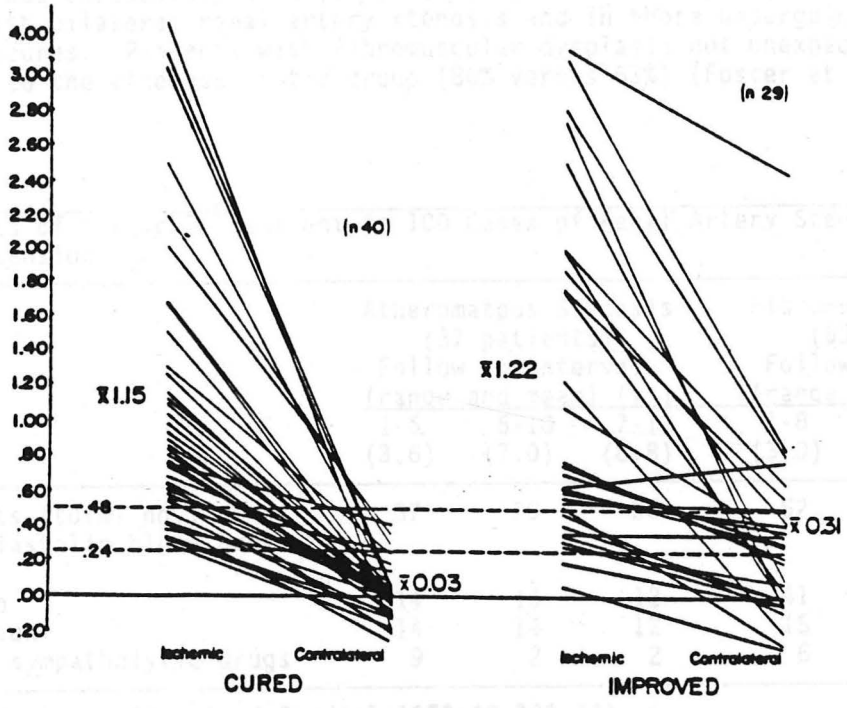
It is our task to calculate the probabilities of that event.

------ Homer Smith, 1948

The surgical revascularization techniques have improved considerably in most centers treating patients with renovascular hypertension. There are no uniformly accepted criteria for the selection of patients for surgical therapy. With proper selection and expert care, operative morbidity is considerably reduced with negligible mortality (Novick et al, 1981; Fry and Fry, 1982; Novick et al, 1987; Dean, 1985; Sellars et al, 1985; Bardam et al, 1985; Dean, 1986; Libertino, 1984; Lawrie et al, 1980; Dean et al, 1984). An aggregate analysis of these and other data attest to the excellent long-term benefits accrued from renal revascularization.

Although revascularization and other surgical techniques are more likely to help patients with lateralizing renal vein renin ratio, the decision to operate is based on the individual assessment of the patient by considering multiple factors. As we have discussed earlier, a number of patients may benefit from relief of renal ischemia although the renin ratio may be less than 1.5 (Figure 23).

Figure 23: Renal: systemic renin indices, comparing individual renal renin activity with systemic renin activity. Mean ischemic kidney indices were similar in cured and improved cases. The mean contralateral index in cured cases revealed marked renin suppression that was significantly less ($p < .01$) than the index reflecting nonsuppression in improved cases. (From Stanley and Fry, Arch Surg 1977;112:1291.)



In the earlier experience with large number of patients with renal arterial lesions, Dustan and colleagues reported the results of 131 patients (99-operated, 32-medically treated) (Dustan et al, 1963). Fifty-eight percent of the operated group were either cured or showed an improved blood pressure control, whereas in the medically treated group, blood pressure control was achieved only in 41%. The operative mortality was 10%. Criteria for medical treatment were essentially the then prevalent contraindications for surgery - age, coronary disease, cerebrovascular disease, renal dysfunction, etc. And the choices of medical treatment were limited to few drugs. A few years later, Peart reported that medical treatment and surgical repair were of equal value (Peart, 1967) and that the operative mortality was an unacceptable 13%. Both the Dustan and Peart studies were not randomized. Thus comparative outcomes are not valid and the results do not support either method of treatment. A similar analysis of medical and surgical treatment was provided by Owen (Owen, 1973). Like previous studies, the groups were not randomized, patients assigned to medical treatment were unsuitable for surgery. In the surgical group, 57% were cured or showed an improvement in blood pressure control; only 37% of the medically treated group showed improvement. The death rate in both groups was alarming - 27% in the

surgically treated group versus 34% in the medically treated group. Additional retrospective analyses from other centers revealed a similar outcome (Shapiro et al, 1969; Bergentz et al, 1969). The results of the Co-operative Study (Franklin et al, 1975) reflect the surgical outcome in 502 patients. They demonstrated a slightly better mortality rate (5.9%) although this is considerably greater than what can be accomplished today. Most operative deaths occurred in the atherosclerotic group. In patients with compromised renal function or coronary disease, the mortality was excessively high (22%). The authors noted a high mortality rate in patients with bilateral renal artery stenosis and in those undergoing complex surgical procedures. Patients with fibromuscular dysplasia not unexpectedly fared well compared to the atherosclerotic group (80% versus 63%) (Foster et al, 1975).

Table 28: Results of Surgical Treatment in 100 Cases of Renal Artery Stenosis with Hypertension

	Atheromatous Stenosis (37 patients) Follow-Up Interval (range and mean) (yr)			Fibromuscular Stenosis (63 patients) Follow-Up Interval (range and mean) (yr)		
	1-6 (3.6)	5-10 (7.0)	7-12 (8.8)	1-8 (3.0)	5-12 (7.0)	7-14 (8.8)
Surviving patients (total no.)	37	29	26	62	60	58
Survivors with diastolic blood pressure < 90 mm Hg						
No medication	14	13	12	41	39	39
Mild medication	14	14	12	15	16	15
Survivors taking sympatholytic drugs	9	2	2	6	5	4

(From Hunt JC and Strong CG: Am J Cardiol 1973;32:562-74)

Table 29: Results of Medical Treatment in 114 Cases of Renal Artery Stenosis with Hypertension

	Atheromatous Stenosis (44 patients) Follow-Up Interval (range and mean) (yr)			Fibromuscular Stenosis (70 patients) Follow-Up Interval (range and mean) (yr)		
	1-8 (3.8)	5-12 (7.1)	7-14 (9.0)	1-8 (3.9)	5-12 (7.2)	7-14 (9.1)
Patients who died	3	16	27	0	5	12
Patients operated on	2	7	7	2	9	9
Patients surviving with medication	39	21	10	68	56	49
With good control of blood pressure*	33	15	9	59	48	43
With poor control of blood pressure	6	6	1	9	8	6

*Diastolic blood pressure < 100 mm Hg most of the time.
(From Hunt JC and Strong CG: Am J Cardiol 1973;32:562-74)

I should mention in this context that most studies including the Co-operative trial consider cure as a blood pressure of 140/90 or less off all antihypertensive medications, improvement as a 15% reduction in post-operative diastolic blood pressure on medications, and failure meaning a no change in the blood pressure. These definitions are not universally applicable because of inconsistences in reporting the follow-up evaluation. Before analyzing the impressive recent surgical experience from this center as well as from the other institutions, I want to mention the Mayo Clinic study which ushered in a new attitude in our understanding of renovascular hypertension (Hunt and Strong, 1973) (Tables 28 and 29). This study included 214 patients with renovascular hypertension who were followed carefully for a period of 8 years. Patients with significant renal impairment - GFR < 50 ml/min, serum creatine > 2.0 (females) or > 2.5 (males) and those with history of atherosclerotic morbid events were excluded from analysis. All patients were initially treated medically and then received continued medical therapy (114 patients) or were operated upon (100 patients). Both treatment modalities were effective in decreasing the morbidity and mortality. Eighty-four percent of the operative group were alive at the time of analysis compared to 66% in the medically treated group. The comparison with atherosclerotic groups provides more striking outcomes. In the medically treated group 62% died compared with the 30% in the surgical group, reflecting the progressive nature of atherosclerotic renal disease. Why is the Mayo experience so important in our attitudes to renovascular hypertension. First, functional criteria were used to define renovascular hypertension. Second, the operative mortality was zero in sharp contrast to the previously noted high mortality. Another landmark study is the report of Dean and colleagues from Vanderbilt (Dean et al, 1981). These workers reported the clinical outcome of 41 patients with renovascular hypertension who were treated medically with a follow-up period 19-33 months. The results are shown in Table 30. In 19 patients, serum creatinine increased between 25% and 120%. GFR fell between 25 and 50% in 12 patients. Renal length decreased in 37%. Progression to total occlusion of the renal artery stenosis was noted in 12%. An operation had to be performed in 41% because of rapid decline in renal function or renal size. It should be emphasized that these events occurred despite good blood pressure control. This study appropriately stresses the value of serial renal function studies in patients receiving medical treatment. In addition to the usual parameters, I wonder if renal scans may be a useful guide in this regard.

Table 30: Frequency of Severe Deterioration in Paramters of Renal Function During Drug Therapy (41 Patients)

Parameter	Patients Followed	Follow-Up, mo.	Failed Event	No. Affected	% Affected
Renal length	38	33	≥10% decrease	14	37
Serum creatinine level	41	25	≥100% increase	2	5
Glomerular filtration rate or creatinine clearance	30	19	≥50% decrease	1	3
Total	41			17	41

The magnitude of benefit from operation for renovascular hypertension has remained controversial for many years and continues to be a source of discussion. Doubts about the benefits relate to the operative risk, frequency of cure rate, and the rate of technical failure. These arguments were persuasive until the availability of cumulative surgical results. Owing to divergent views, the Co-operative Study was undertaken, which suffered from the lack of uniformity and a mixture of operative techniques. Although initiated to resolve the prevalent controversies, the conclusions of the Co-operative Study underscored the heterogeneity of diagnostic tests and a multitude of factors affecting the surgical outcome. Fortunately, the subsequent reports from the University of Michigan, University of California at San Francisco, Mayo Clinic, Cleveland Clinic and the Southwestern Medical School have confirmed the long-term safety and efficacy of operative treatment of renovascular occlusive disease. In the 55 consecutive patients treated for atherosclerotic renal vascular disease at this institution, 93% of patients were cured or improved (Fry, personal communication). The mean post-operative follow-up blood pressure was 139/83 mm Hg compared to the pre-operative blood pressure of 202/111 mm Hg. There was one operative death due to hemorrhagic pancreatitis.

Table 31: Results of Operative Treatment

Center	No. of Patients	% Cure	% Improved	% Failed	% Operative Mortality
Fibrodysplastic lesions					
University of Michigan[A]	144	55	39	6	0
University of California San Francisco[B]	77	66	32	1.3	0
Vanderbilt University[E]	56	77	19	1	0
University of Lund[C]	40	66	24	10	0
Atherosclerotic lesions					
Vanderbilt University[E]					
Renovascular alone	126	31	62	7	1
Aortic and renal surgery	50	9	72	21	12
University of Michigan[A]					
Focal renal lesions	64	33	58	9	0
Diffuse atherosclerosis	71	25	47	28	8.5
Cleveland Clinic[D]	78	40	51	9	2.0

[A] Stanley et al, 1982
[B] Stoney et al, 1981
[C] Bergentz et al, 1979
[D] Novick et al, 1981
[E] Dean et al, 1983

In general, the operative results in patients with fibromuscular disease are predictably favorable with amelioration of hypertension and with minimal surgical risk. Results of atherosclerotic vascular disease are more complex but the operative risk is acceptable when the procedure

is performed by expert vascular surgery groups. For example, Dean noted only one operative death in a group of 126 patients undergoing renal revascularization (Dean, 1983). Stanley and co-workers experienced 8.5% operative mortality in 71 patients with diffuse atherosclerotic disease. The operative mortality among patients with extensive atherosclerotic disease can be expected to be somewhat higher compared to those with limited or focal atherosclerotic lesions (Dean et al, 1984). Dr. Fry reported excellent operative results in 22 patients with extensive atherosclerosis (Fry and Fry, 1982). The post-operative blood pressure was reduced to 136/81 mm Hg from the pre-operative level of 211/123. It should be noted that no operative deaths occurred in this experience once again reminding us about the role of experienced vascular surgeons in influencing the ultimate outcome. These results contrast with those obtained more than a decade ago. Stanley and Fry in 1977 reported a higher rate of mortality in patients with generalized atherosclerosis (Stanley and Fry, 1977). The impact of severity of atherosclerotic disease on the ultimate outcome has been demonstrated by the Vanderbilt and Michigan experiences. At Vanderbilt, atherosclerotic disease requiring renal revascularization was associated with 31% and 61% cure and improvement rate, respectively (Dean et al, 1984). When renal revascularization was combined with aortic surgery the cure and improvement rates changed to 9% and 72%, respectively. The Michigan experience showed similar trends (Stanley et al, 1982). Renal revascularization in patients with focal atherosclerotic disease resulted in a 33% cure rate compared to an improvement in 58%. However, the response rate shifted to a 25% cure and a 47% improvement rate in patients with generalized vascular disease.

LONG-TERM FOLLOW-UP OF OPERATED PATIENTS

Obviously the benefits of surgical treatment should be measured by the long-term follow-up evaluation of patients in terms of blood pressure control and renal function. The results must also be analyzed within the context of the pathological diagnosis and whether the disease was unilateral or bilateral.

Table 32: Medical versus surgical treatment of renovascular hypertension

	Surgical 100 Pts. (%)	Medical 100 Pts. (%)
Well, 1 yr	99	98
Well, 10 years	78	36

(From Kaufman, 1979)

Table 33: Surgical revascularization technique for renal artery disease at the Cleveland Clinic (1975-84)

	Atherosclerosis (n = 254)	Fibrous dysplasia or aneurysm (n = 126)
Aortorenal bypass	138	82
Splenorenal bypass	42	4
Hepatorenal bypass	29	0
Iliorenal bypass	19	0
Autotransplantation	8	1
Aortic replacement	11	0
Ex vivo repair and autotransplantation	0	37
Other	7	2

Table 34: Results of surgical revascularization for renovascular hypertension at the Cleveland Clinic (1975-84)

	Number patients	Postoperative blood pressure			Follow-up (months)
		Cured	Improved	Failed	
Atherosclerosis	180	55 (31%)	110 (61%)	15 (8%)	6–117
Fibrous dysplasia	104	66 (63%)	31 (30%)	7 (7%)	10–115

Novick analyzed the extensive experience with surgical revascularization at the Cleveland Clinic (Novick, 1987) (Tables 33 and 34). In 380 revascularization procedures performed during a 10 year period, the operative mortality was 2.1% in patients with atherosclerotic disease and zero in patients with fibromuscular dysplasia. Hypertension was cured in a remarkable 92% of patients with atherosclerotic disease and in 93% of patients with fibrous dysplasia. Importantly, the renal function was preserved or improved in 89% of patients who were operated, mainly to improve renal function. Similar results particularly in patients with fibromuscular dysplasia have been reported from other referral centers (Ernst et al, 1972; Stoney et al, 1981; Straffon and Siegel, 1975; Starr et al, 1980).

Table 35 : Sequential 1-23-Year Follow-up Arteriography (198 Reconstructions)

STATUS	NO. OF GRAFTS	%
No adverse change	174	88
Aneurysmal dilation	7	3.5
Stenosis	10	5.0
Occlusion	4	2.0
False aneurysm	3	1.5

(From Dean RH et al: Sugery 1985;44-52)

During a 20 year follow-up period, actuarial patient survival at 5 years was 93%, at 10 years 80%, and at 20 years 70 % (Starr et al, 1980). Amazingly, 74 percent remained normotensive at 15 years. A 15-23 year follow-up of patients showed the durability of operative results (Dean et al, 1984) (Table 35). The initial blood pressure response (1-6 months) indicated 44% were cured and 40% improved and no change was demonstrated in the remaining 16%. Sequential clinical and functional status over the long-term follow-up period was obtainable in 66 patients. Follow-up to date revealed that overall benefit from the surgery persisted although there was a decrease in the percentage of patients who sustained a cure. The mortality and morbidity during the follow-up was assessed by Kaplan-Meier life tables and Cox's proportional hazards regression analysis to identify pre-operative risk factors that would predict surgical benefits - e.g. focal versus generalized atherosclerosis, CAD, LVH, azotemia, smoking, diabetes, and hyperlipidemia. The risk factors that were significant in determining earlier death after the operation were LVH and CAD. The most significant factor was generalized atherosclerosis. The limited patient population did not permit consideration of statistical significance for other pre-operative risk factors.

Taken together these results indicate the value of operative treatment in properly selected patients with renovascular hypertension (Table 36). The surgical benefits are inversely proportional to the duration of hypertension (Table 37). Therefore, the decision to postpone operative treatment indefinitely should not be made without a good reason.

Table 36: Results of Surgical Series for Treatment of Renovascular Hypertension.

	No. of Patients	Cured (%)	Improved (%)	Failed (%)	Deaths (%)	Nephrectomy (%)
Atheroma (all)	969	38	42	20	3.9	14.9
Focal.	382	42	46	13	0	?
Diffuse	435	24	45	36	8.8	7.6
Fibromuscular	663	59	30	11	<1	?

* Data from Pickering TG, Sos TA, Laragh JH: *Am J Med* 77:61, 1984.

Table 37: Surgical cure in patients with known technically satisfactory operations and not receiving renin-suppressing medications during RVR test.* (Data from Hughes JS et al: Am Heart J 1981;101:408-13).

	Hypertension duration			
	<5 years	*≥5 years*	*Total*	
RVR ratio ≥ 1.4	11/11 (*100%*)	0/2 (*0%*)	11/13 (*85%*)	$p < 0.02$
RVR ratio < 1.4	2/4 (*50%*)	0/3 (*0%*)	2/7 (*29%*)	
Total	13/15 (*87%*)	0/5 (*0%*)	13/20 (*65%*)	
	$p < 0.001$			

*Number of patients and success rate.

SURGICAL TECHNIQUES: A variety of renal revascularization procedures are available for treating renovascular hypertension. However, aorto-renal bypass with autogenous saphenous vein or arterial graft is the preferred technique in most centers (Figure 24). Revascularization is more complicated when branch vessels are involved or when multiple renal arteries supplying a kidney are occluded. Aorto-renal bypass with a synthetic material is indicated only when autogenous vascular graft is not available or when adjunctive aortic replacement is performed. While the Dacron grafts provide a satisfactory result, there is an increased tendency for early post-operative thrombosis (Kaufman, 1975). When both the renal arteries are stenosed, it is preferable to operate on one side first since bilateral renovascular repair results in greater morbidity. The most stenotic side or the side with lateralizing renin secretion is chosen for initial repair. The opposite side can be operated subsequently if hypertension persists or recurs following successful unilateral revascularization.

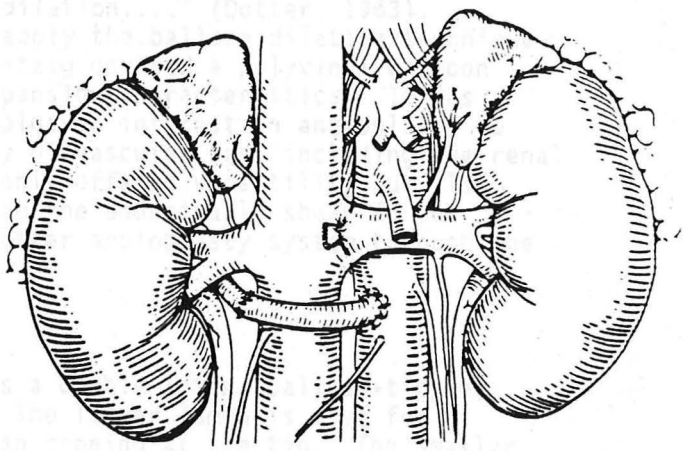


Figure 24: Sketch illustrating the technique of aortorenal bypass. The bypass graft is anastomosed end-to-side to the aorta and end-to-end to the distal renal artery.

Nephrectomy should be avoided whenever possible as a treatment modality for renovascular hypertension. Improved revascularization procedures have virtually eliminated the need for nephrectomy in patients with renovascular hypertension. However, total or partial nephrectomy retains a role in patients with completely occluded atrophic kidney, non-correctible renovascular lesions such as large aneurysms, and diffuse renovascular disease, etc. Occasionally, nephrectomy may be the procedure of choice in patients with poor surgical risk who have a normal contralateral kidney. In properly chosen patients, the results of nephrectomy are comparable to results obtained with revascularization procedures (Novick, 1984).

The other operative technique - splenorenal bypass, hepatorenal bypass, ileorenal bypass, extracorporeal reconstruction and autotransplantation - are performed in complex situations.

B. PERCUTANEOUS TRANSLUMINAL RENAL ANGIOPLASTY (PTRA)

PTRA or "balloon dilation" has become an alternative to surgical and medical treatment of renovascular hypertension. The principle involved is mechanical dilation of the stenotic artery with an inflatable balloon catheter placed in the renal artery utilizing Seldinger technique.

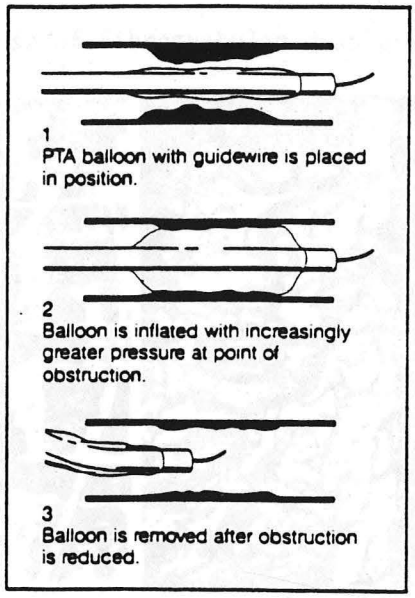
A brief historical perspective of PTRA is in order. The first transluminal angioplasty was performed by Dotter inadvertently in 1963 when he threaded a catheter in a retrograde fashion through an occluded iliac artery to perform abdominal angiography (Dotter, 1980). At a radiology meeting, Dotter commented: "perhaps it is wishful thinking, but in any event I am convinced that the relief of atheromatous obstruction in small arteries can best be accomplished by catheter technics. A flexible guide introduced percutaneously into an artery proximal to an area of atheromatous narrowing can be manipulated so as to traverse the obstruction. A mechanical attack upon the lesion would then become feasible, perhaps by gradual direct dilation...." (Dotter, 1963). However, it was left to Gruntzig to apply the balloon dilation technique prospectively (Gruntzig, 1976). Gruntzig devised a polyvinyl balloon catheter with unique flexible and expansion characteristics. It was Gruntzig's work that triggered an explosive interest in angioplasty to relieve stenotic lesions in a variety of vascular beds including the renal arteries. The balloon catheter not only offered versatility but also provided a clear advantage in avoiding the undesirable shear forces associated with the passage of the Dotter angioplasty system through the stenotic blood vessel.

THE TECHNIQUE OF PTRA

The Gruntzig balloon catheter is a double-lumen, balloon-tipped, single-end-hole polyvinyl catheter. The larger lumen is used for introducing contrast medium through an opening at the tip. The smaller lumen leads into the distensible balloon segment. The procedure is performed in the radiology suite using the Seldinger technique. The balloon catheter is maneuvered so that the balloon is directly across the stenosis. The balloon is then inflated with a pressure manometer to the desired pressure (usually 5 atmospheres) (Martin and Casarella, 1984) (Figure 25). The balloon may be inflated several times until the pressure gradient across the stenosis drops (Figure 26) and a satisfactory anatomic appearance is confirmed. Following the procedure, the patient should be closely monitored for blood pressure, urine output, and bleeding from the arterial puncture size. With successful balloon dilation, the blood pressure usually falls in about 4-6 hours. I have seem impressive falls in blood pressure within a few minutes after the procedure. The value of anticoagulation during PTRA is unclear but some routinely recommend systemic heparinization (Schwarten, 1987). In patients with atherosclerotic lesions, it is a common practice to use aspirin and dipyridamole after the PTRA for an indeterminate period. There are no particular guidelines concerning the value and duration of anti-platelet therapy following PTRA.

Figure 25:

Diagrammatic representation of standard PTA procedure.



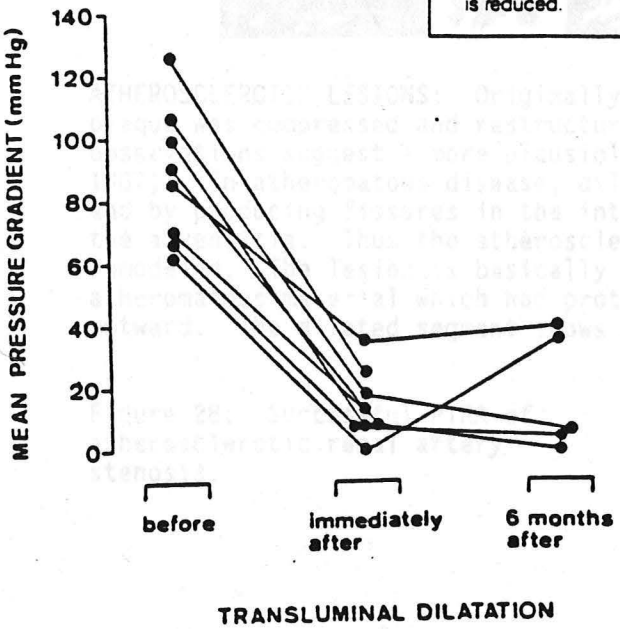


Figure 26: Mean pressure gradients across the renal-artery stenosis before (89±22.8 mm Hg) and immediately after (14.3±11.2 mm Hg) percutaneous transluminal dilatation in eight patients with left-sided renal-artery stenoses. Determination of pressure gradients was repeated after 6 months (mean, 16±18.5 mm Hg) in five patients.

MECHANISM OF RENAL ANGIOPLASTY

Although with an inflatable balloon the stenotic lesion can be dilated, it is interesting to ponder how a stenosis can be relieved, remolded, and remain dilated after a mechanical procedure.

FIBROMUSCULAR DYSPLASIA: These lesions dilate easily at low balloon pressures. Presumably, application of an expanding force causes disruption of the collagenous ridges and possible compression of the hyperplastic intima. The components of the stenotic lesion do not recoil immediately but healing of the lesion takes place in the dilated state.

Figure 27: Response of fibromuscular dysplastic lesion to PTRA.

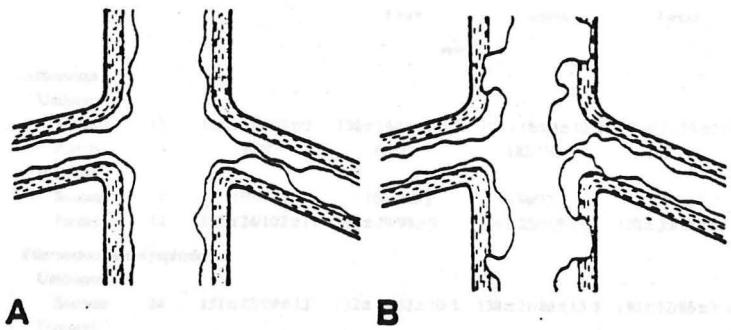
ATHEROSCLEROTIC LESIONS: Originally it was thought that atheromatous plaque was compressed and restructured by the dilation process. Recent observations suggest a more plausible explanation (Sos and Pickering, 1987). In atheromatous disease, dilation occurs by rupturing the plaque and by producing fissures in the intima and media and by overdistending the adventitia. Thus the atherosclerotic material is displaced and remodeled. The lesion is basically turned inside out, i.e. the atheromatous material which had protruded into the lumen now projects outward. The dilated segment shows decreased contractility.

Figure 28: Successful PTRA of atherosclerotic renal artery stenosis.

ANATOMIC CLASSIFICATION OF RENAL ARTERY STENOSIS FOR PTRA

Cicuto and associates from the Hospital of University of Pennsylvania have provided a useful morphologic description of atherosclerotic renal artery lesions with reference to their response to PTRA (Cicuto et al, 1981) (Figure 29). The lesions were classified as renal, aortic, or mixed; renal - the luminal narrowing begins beyond a patent ostium, i.e. the stenosis is within confines of the renal artery; aortic - the renal artery contiguous with the aorta is obstructed and mixed. The renal lesions respond well to PTRA whereas the aortic and mixed lesions respond poorly or not at all to PTRA. These findings are not at all surprising. The fluoroscopic observations revealed that the angioplasty balloon may displace the aortic plaques only to return to their original position in aortic and mixed lesions. In the pure renal lesions, as the balloon is inflated its expansion is sustained circumferentially within the renal artery. This anatomic classification of atherosclerotic plaques is useful in predicting response to PTRA. Patients with pure renal lesions have a better chance of benefit from PTRA compared to those with aortic or mixed lesions.

Figure 29: Lesions compromising renal blood flow. A, Renal artery lesion. Obstructing plaque (stippled area) lies completely within confines of renal artery. B, Aortic lesion. Large aortic, atherosclerotic plaques overhang ostium of renal artery compromising blood flow. No Significant stenosis within renal artery itself. (From Cicuto KP, et al: Am J Roentgen 1981;137:599-601).



PATIENT SELECTION FOR PTRA

The main indication for PTRA presently is renovascular hypertension but this procedure is being increasingly utilized to relieve renal artery stenosis in patients with renal insufficiency (Sos and Pickering, 1987). Fibromuscular and non-ostial focal atherosclerotic lesions respond best to PTRA. The success rate is low for occluded renal arterial lesions, ostial stenoses and bilateral involvement. Relative contraindications include renal artery aneurysms and renal artery dissection. PTRA of renal artery lesions without pathophysiological significance remains controversial. Natural history of renal artery stenosis, atherosclerotic and to a lesser extent fibromuscular dysplasia, has shown that the occlusive disease may progress resulting in complete occlusion occasionally. For this reason,

some advocate PTRA intervention. It could be argued that hemodynamically insignificant lesions should be left alone. No unanimity exists concerning this issue at the present time.

RESULTS OF PTRA

The results of PTRA in terms of initial success rate, the durability of success and favorable blood pressure response depend on the pathology of the stenotic lesion.

The immediate and long-term results of PTRA in fibromuscular dysplasia are uniformly good. In a series of 100 patients treated by PTRA, recurrent stenosis was not seen during a follow-up period up to 8 years (Schwarten, 1987). Similar favorable results have been reported in other large series (Pickering et al, 1984a; Kuhlmann et al, 1985; Milan et al, 1979; Sos et al, 1983; Tegtmeyer et al, 1982) (Table 38). Young patients with hypoplastic renal arteries and those with ostial renal artery stenosis show a poor response to PTRA. The success rate of PTRA in patients with fibromuscular dysplasia is close to 90-92%.

Table 38: Effects of Successful Renal Angioplasty on Blood Pressure.* (From: Sos TA et al: NEJM 1983;309-274-9.

	No. of Patients	Blood Pressure (Systolic/Diastolic) †			
		Before Angiography	After Angiography		
			1 Day	1 Month	1 Year
			mm Hg		
Atheroma					
Unilateral					
Success	17	166±18/100±9	136±14/83±13 ‡	151±18/89±10 §	150±31/89±12 ¶
Partial	3	190/97	162/90	182/102	180/114
Bilateral					
Success	2	197/103	164/100 ‖	134/72 ‖	159/90 ‖
Partial	12	187±24/102±11	187±29/98±9	194±25/109±17	170±30/95±15
Fibromuscular dysplasia					
Unilateral					
Success	24	152±22/99±13	132±16/82±10 ‡	138±21/86±13 ‡	130±12/86±7 ‡
Bilateral					
Success	3	163/98	128/75 ‖	130/76 ‖	133/80 ‖

*Patients with unsuccessful angioplasty were excluded from this table.
†Values are expressed as means ±S.D.
‡P<0.001 by t-test as compared with blood pressure before percutaneous transluminal renal angioplasty.
§P<0.01. ¶P<0.05. ‖All patients had a decrease in blood pressure.

ATHEROSCLEROTIC LESIONS

In patients with non-ostial atherosclerotic focal atherosclerotic lesions, PTRA has yielded satisfactory results in terms of blood pressure control and potency of dilation (Mahler et al, 1982; Geyskes, 1983; Schwarten, 1987, Pickering et al, 1984a). The results are less favorable in patients with diffuse atherosclerotic disease and ostial stenosis. Long-term clinical results with PTRA in atherosclerotic renal artery stenosis are shown in Tables 39 and 40.

Table 39: Results of Percutaneous Balloon Angioplasty for Renovascular Hypertension (4-Month to 4-Year Follow-up)

	No of Patients	Cured (%)	Improved (%)	Failed (%)	Deaths (%)	Nephrectomy (%)
Geyskes et al, 1983	70	20	41	31	1	0
Sos et al, 1984	82	28	24	48	0	2
Tegtmeyer et al, 1984	98	26	67	7	1	0
Miller et al, 1985	63	-75-		12	2	2

(From Grüntzig A, Vetter W, Meier B, et al: Lancet 1:801, 1978)

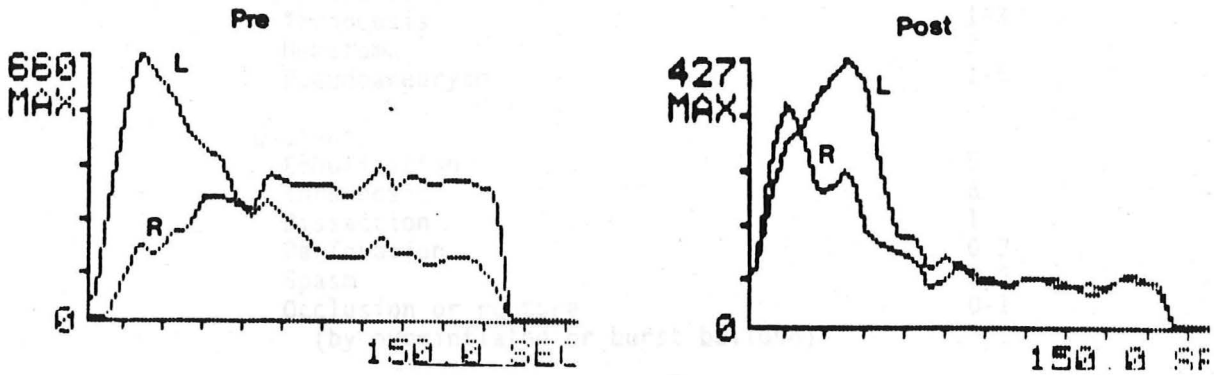
Table 40: Results of Angioplasty Series for Treatment of Renovascular Hypertension. (From Pickering TG et al: Am J Med 1984a;77:61-6)

	Cured (percent)	Improved (percent)	Failed (percent)	Deaths (percent)	Nephrectomy (percent)	Number	References
Atheroma							
	13	63	25	0	0	8	[20]
	44	48	8	0	0	52	[21]*
	35	57	8	0	0	24	[22]
	9	43	48	2	0	44	[23]
	4	36	60	20	20	25	[24]†
	25	45	30	0	0	20	[2]‡
Fibromuscular							
	83	17	0	0	0	6	[20]
	67	33	0	0	0	13	[22]
	48	48	5	0	0	21	[23]
	47	35	18	0	6	17	[24]
	59	33	7	0	3	27	[2]

*Not all patients had atheromatous stenoses.
†Results for four-year follow-up.
‡Results for complete and partial success in unilateral disease.

In the Cornell series, renal artery stenosis was caused by atheroma in 51 of 89 patients (57%) who were followed for at least two years after PTRA. None of 5 patients with ostial stenosis showed any improvement in blood pressure. The overall technical success rate among atheromatous patients was 33%. The most common reason for a failed procedure was inability to pass the guide wire or catheter across the lesion. Although these workers reported a 82% success rate as assessed at 3 months after PTRA in patients with unilateral atherosclerotic lesions, this figure is misleading when it is recalled that successful angioplasty was not possible in 67% of the entire group of 51 patients. The renal vein renin ratio served as a predictor of response to PTRA in this study. On the other hand, Kuhlmann et al in their 60 patients subjected to renal vein renin studies concluded that renal vein renin activity was not a prognostic indicator. They believe that renal vein renin determination should not be considered obligatory in the evaluation of patients for PTRA.

Figure 30: Renogram time-activity curves before angioplasty demonstrate abnormally prolonged vascular phase with peak activity (T-max) in right (R) kidney, occurring at 11 minutes, with return to normal postangioplasty (T-max 5 minutes). (From Gupta S et al: Clin Nucl Med 1985;10:380-4).



In summary, PTRA has added a new dimension to our management of patients of renovascular hypertension. Whether PTRA bestows the same long-term benefits as surgical revascularization is not known. Clearly it is an attractive therapeutic procedure of choice for patients with fibromuscular dysplasia and with focal atherosclerotic non-ostial lesions. Further prospective experience and comparative analysis against surgical results are necessary to assign a more categorical role for PTRA.

COMPLICATIONS OF PTRA

In experienced hands, complication results from PTRA is low. For example, in 433 PTRA procedures, not a single instance requiring emergency operation occurred in Schwarten's experience (Schwarten, 1987). Tegtmeyer reported 12 major complications in 166 PTRA procedures (Tegtmeyer et al, 1984). Four percent of patients developed hematoma (Pickering et al, 1984b). Transient deterioration of renal function can occur in 2% of the cases due to a combination of dye load and the procedure itself. Perhaps the most common complication with PTRA is dissection of the renal artery (Sos et al, 1983) occurring in 5% of the cases. Some but not all patients experiencing this complication require revascularization. Rupture of the renal artery is a rare and most dreaded complication. Therefore, expert surgical backup is essential whenever PTRA procedure is performed. I have seen 2 patients with renal artery rupture following PTRA and both survived because of immediate surgical intervention (within 30 minutes). Distal embolization has been reported rarely. PTRA has been proposed as an alternative to surgery in patients who have operative risks. Ironically, certain complications of PTRA require immediate surgical intervention.

Table 41: COMPLICATIONS OF PTA (From Sos TA et al, NEJM 1983;309:274-9)

Complications of PTA	Incidence (%)
Puncture site	
Thrombosis	1-3
Hematoma	2
Pseudoaneurysm	1-5
Distant	
Embolization	5
Thrombosis	5
Dissection	1
Perforation	0-3
Spasm	0-5
Occlusion or rupture (by overinflated or burst balloon)	0-1

PTRA TO PRESERVE RENAL FUNCTION

Since renal function may be impaired in patients with unilateral or bilateral renal artery stenosis, PTRA may have an impact on renal function. Madias and colleagues noted stabilization or improvement in renal function of 7 of 11 patients with severe hypertension and renal impairment (Madias et al, 1982). Interestingly, stabilization or improvement in renal function was observed in some patients even if no effect on blood pressure occurred (Kremer et al, 1986). More recently, Pickering and co-workers reported the influence of PTRA in 45 patients with atherosclerotic renal artery stenosis and progressive azotemia (Pickering et al, 1987). In 26 patients (47%) there was a significant and sustained reduction in serum creatinine over a 2-3 year follow-up. In a group of patients undergoing PTRA for hypertension or for hypertension associated with azotemia, Bell et al report a significant improvement in renal function of 8 patients; in 3 patients the renal function worsened and in the remaining 16 it remained unchanged. Together the above results suggest that an improvement in renal function can be expected for PTRA in azotemic patients with renovascular disease. As one would anticipate following successful PTRA, effective renal plasma flow increases (Teates et al, 1983).

PTRA IN COMPLEX SITUATIONS

PTRA has been utilized to treat transplant renal artery stenosis (Lohr et al, 1986; Neithamer et al, 1986). More than 90 patients with transplant renal artery stenosis treated with PTRA were followed for periods up to 72 months. PTRA was successful in 84% of cases with graft loss in one patient and renal artery perforation occurred in another patient.

Limited preliminary experience indicates that PTRA may be useful in the treatment of patients with totally occluded renal arteries (Sniderman

and Sos, 1982) and in patients with renal artery stenosis in a solitary kidney (Weinberger et al, 1979). PTRA has been shown to be effective in the treatment of children with renovascular hypertension (Saddenki, 1987; Awazu et al, 1986).

C. COMPARISON OF PTRA VERSUS SURGICAL TREATMENT OF RENOVASCULAR HYPERTENSION

There have been no randomized clinical trials assessing the benefits and risks of PTRA compared with surgical treatment in the long-term management of renovascular hypertension. Pickering compared the results of PTRA with results from several surgical series (Pickering et al, 1984a). From the retrospective analysis of heterogenous study patients, they concluded that results with PTRA are as good as those with surgery in patients with fibromuscular dysplasia and that for patients with atheroma the success rate is better with surgery. There are obvious pitfalls in comparing the relatively new PTRA technique with relatively old surgical series. For example, it is unfair to use the surgical results from the Co-operative Study which consisted of patients who were operated upon in the 1960s. It is probable that a greater percentage of patients in PTRA series had a more easily treatable focal atherosclerotic lesions than in the referred surgical series in which only 40% of 969 patients had focal atheromatous diseases. In the experienced hands, the operative benefit rate for surgical treatment exceeds 90% with negligible mortality.

Kuhlmann and associates reported that PTRA bestowed an overall benefit rate of 82% in patients with fibromuscular dysplasia (Kuhlmann et al, 1985). This figure should be contrasted with recent surgical series (discussed in the surgical management section) with a benefit rate of 94% and zero mortality. The overall benefit rate from PTRA in patients with atherosclerotic stenosis was 77% during the 21.6 months follow-up. Contrast this number with the recent surgical series which render a much higher benefit for a more prolonged period. In order to derive a more meaningful judgement, prospective trials should be done comparing the two techniques in properly selected patients with similar anatomic and hemodynamic traits.

D. MEDICAL TREATMENT OF RENOVASCULAR HYPERTENSION

Although the most dependable treatment for renovascular hypertension is relief of ischemia by means of PTRA or surgery, medical treatment has a role in the management of many patients with this disorder. Medical treatment is necessary to provide optimal blood pressure control prior to planned surgery or angioplasty. It is also indicated in patients who are unwilling or unable to undergo a corrective procedure because of poor general health. And of course, medical management should be provided to patients whose blood pressure is not normalized by surgery or angioplasty. There is still no consensus regarding therapeutic approach to patients in whom the functional significance of renal artery stenosis is less clear. For these patients medical control of hypertension is indicated. Despite the availability of specific and better tolerated antihypertensive drugs, the role of medical therapy is being steadily supplanted by surgery or PTRA. The therapeutic

objectives of medical therapy are two-fold-to control hypertension and to stabilize the renal function. The importance of monitoring these parameters by careful follow-up of patients cannot be overemphasized.

Table 42: Frequency of Severe Deterioration in Aspects of Renal Function. (From: Dean RH et al: J Vasc Surg 1981;1:234-42).

Aspect	No. of Patients Followed Up	Mean Follow-up, mo	Failure Event*	No. Affected	% Affected
Renal length	38	33	≥ 10% decrease	14	37
Serum creatinine	41	25	≥ 100% increase	2	5
Glomerular filtration rate or creatinine clearance	30	19	≥ 50% decrease	1	3

*At least one "failure event" present.

While implementing medical treatment the natural history of renal artery stenosis should be considered. It is evident that not only atherosclerotic but also fibrous dysplastic lesions progress sometimes culminating in total occlusion of the artery. No medical treatment has been ever shown to alter the natural history of arterial disease. The chances of progressive occlusive disease are greater in patients with atherosclerosis. In one follow-up arteriographic study, 63% of patients with atherosclerosis demonstrated progression during a 28 month period (Wollenweber et al, 1968). Similar observations were seen in other follow-up studies (Meaney et al, 1968; Schreiber et al, 1984). Renal function declined in patients with progressive renal arterial disease (Table 42). While progression in patients with fibromuscular dysplasia is somewhat less compared to atheromatous disease, most of such patients are typically young with a prospect of many years of drug therapy. So for patients with fibromuscular dysplasia, surgery or PTRA are the preferred choices.

MEDICAL TREATMENT: PRINCIPLES

In general, the therapeutic principles for the medical management of renovascular hypertension are similar to those for essential hypertension. However, certain factors should be considered in the choice of drug therapy based on the pathophysiology of renovascular hypertension. Since renin-angiotensin system is linked to blood pressure regulation in patients with renal ischemia, special attention should be directed at using drugs that inhibit the renin-angiotensin system, e.g. beta-blockers and ACE inhibitors. The renin-angiotensin mechanism may be especially operative in patients with unilateral renal artery stenosis since this condition is similar to Goldblatt two-kidney one clip hypertension. As discussed elsewhere, renin dependency becomes less prominent the longer hypertension is maintained. Despite this phenomenon, drugs blocking the renin-angiotensin mechanism may still be helpful in lowering the blood pressure levels.

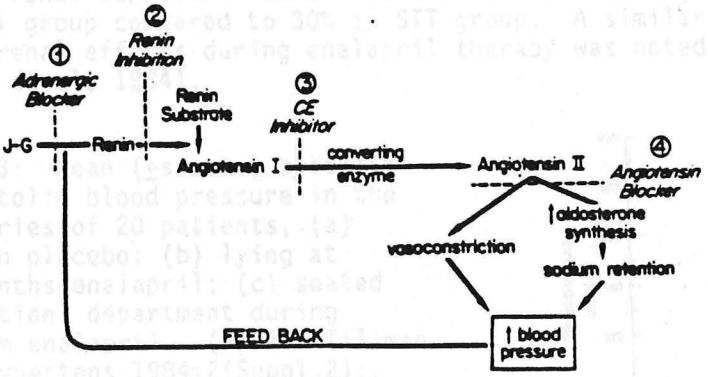
BETA-BLOCKERS:

Beta-blockers inhibit renin release and are effective antihypertensive agents in high and normal renin states including renovascular hypertension (Salvetti et al, 1977). The exact mechanism of their antihypertensive action is not known although it is believed that renin inhibition may be the most important mechanism (Pickering, 1987). Therefore, beta-blockers have been widely used in the long-term management of renovascular hypertension. Although some beta-blockers have been shown to decrease renal blood flow in patients with essential hypertension (Sullivan et al, 1976), they are generally considered to be safe in the long-term treatment.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

The ACE inhibitors have notable antihypertensive and other effects in renovascular hypertension. Besides being therapeutic, captopril administration may also have a diagnostic value in renovascular hypertension (Muller et al, 1986). The dominant mechanism of action of captopril is ACE inhibition resulting in a fall in angiotensin II levels (Figure 31). Since captopril exerts potent inhibitory effects on angiotensin II , it has been claimed that long-term response to captopril is a good predictor of surgical outcome (Staessen et al, 1983; Atkinson et al, 1982). Patients with renovascular hypertension show a salutary blood pressure response to ACE inhibitor therapy (Bauer, 1984; Case et al, 1982b; Hollenberg, 1983; Hollenberg, 1984). Captopril has proven effective in over 80% of 269 patients with renovascular hypertension (Hollenberg, 1983) (Figure 32).

Figure 31: The four sites of action of the currently available inhibitors of the renin angiotensin system.



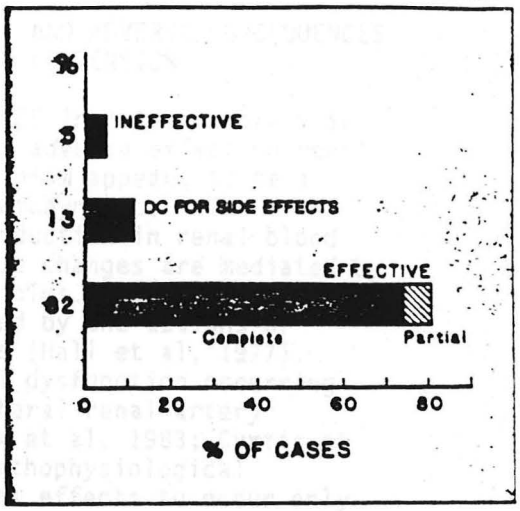


Figure 32: Patient disposition at three months. The treatment with captopril was ineffective in 5% and the drug was discontinued (DC); in 13% captopril had been discontinued because of side effects; the agent was fully effective either alone or with a diuretic in achieveing a diastolic blood pressure of 95 mm Hg in 74%. In the remainder, indicated as "partial," a third agent was employed: goal blood pressure was achieved in about half of the remainder. BP = blood pressure, BUN = blood-urea nitrogen. (From: Hollenberg NK: Cardiovasc Reviews Reports 1983;4:852-76).

Like captopril, the other ACE inhibitor enalapril has also been shown to be useful in the medical management of patients with renovascular hypertension (Hodsman et al, 1983; Jackson et al, 1986; Franklin and Smith, 1985; Tillman et al, 1984) (Figure 33). Although certain pharmacological differences exist between captopril and enalapril, both these drugs exert equal antihypertensive effects in patients with renovascular hypertension. Franklin and Smith compared the results of enalapril plus hydrochlorothiazide therapy with standard triple therapy (STT) in 75 patients with renovascular hypertension. Blood pressure control was greater in the enalapril group. Poor response to therapy occurred mainly in patients with bilateral renal artery stenosis or impaired renal function. Renal function deteriorated in 20% of the enalapril group compared to 30% in STT group. A similar incidence of adverse renal effects during enalapril therapy was noted in another study (Tillman et al, 1984).

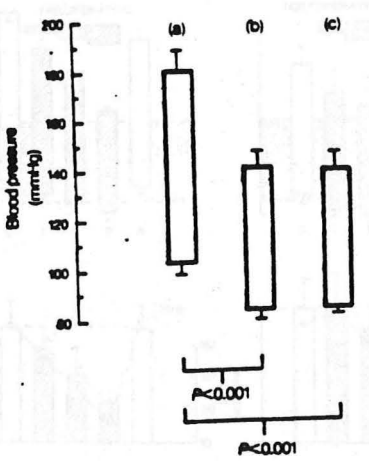


Figure 33: Mean (±s.e.m.) systolic and diastolic blood pressure in the whole series of 20 patients, (a) lying, on placebo; (b) lying at three months enalapril; (c) seated in outpatient department during long-term enalapril. (From: Tillman DM: J Hypertens 1984;2(Suppl 2): 93-100).

THE RENIN-ANGIOTENSIN SYSTEM, RENAL HEMODYNAMICS, AND ADVERSE CONSEQUENCES OF ACE INHIBITION IN PATIENTS WITH RENOVASCULAR HYPERTENSION

Certain clinical observations suggest that ACE inhibitor therapy in the presence of renal artery stenosis may have an adverse effect on renal blood flow and renal function. The precise mechanism appears to be a direct action of these compounds on intrarenal hemodynamics. The intrarenal actions of angiotensin II include a reduction in renal blood flow and to some extent a reduction in GFR. These changes are mediated by constriction of both afferent and efferent arterioles. It is postulated that GFR in the presence of ischemia is maintained by the actions of angiotensin on the efferent glomerular arterioles (Hall et al, 1977). Attenuation of this role by ACE may explain renal dysfunction occurring with ACE inhibitor therapy in patients with bilateral renal artery stenoses or stenosis of a solitary kidney (Hricik et al, 1983; Curtis et al, 1983; Blythe, 1983) (Figure 34). Based on pathophysiological considerations, one would expect the adverse renal effects to occur only with drugs that block the intrarenal actions of angiotensin II. However, experimental infusion of nitroprusside in patients with bilateral renal artery stenosis caused a marked fall in GFR (Textor et al, 1985) (Figure 35). That the impaired renal dysfunction occurs due to dysregulation of the renal-angiotensin system in the ischemic side is now well documented (Miyamori et al, 1986; Jackson et al, 1986) (Figure 36 and 37).

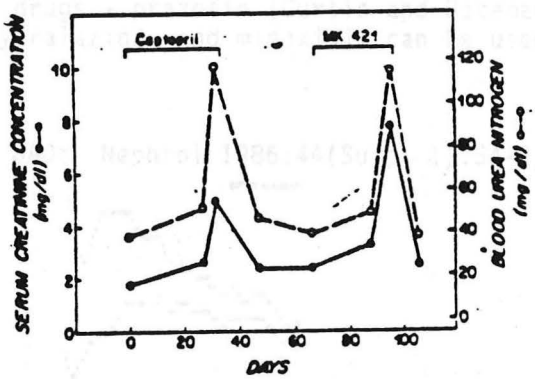


Figure 34: Responses of Serum Creatinine and Blood Urea Nitrogen to the Converting-Enzyme Inhibitors Captopril and MK421 in Patient 2.
To convert creatinine values to micromoles per liter, multiply by 88.4. To convert blood urea nitrogen values to millimoles per liter, multiply by 0.357. (From: Hricik DE et al: NEJM 1983;308:373-6).

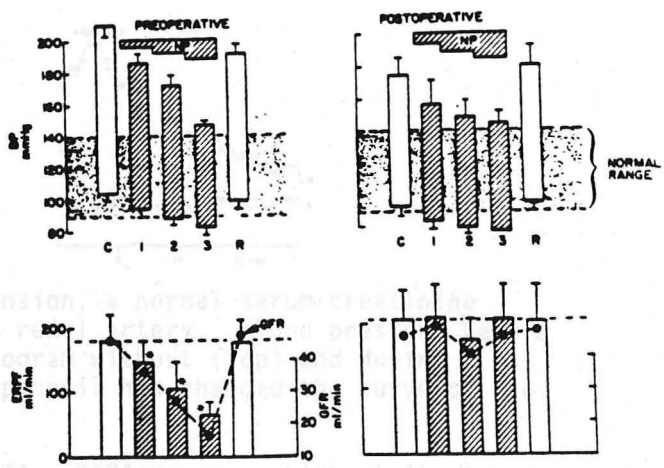
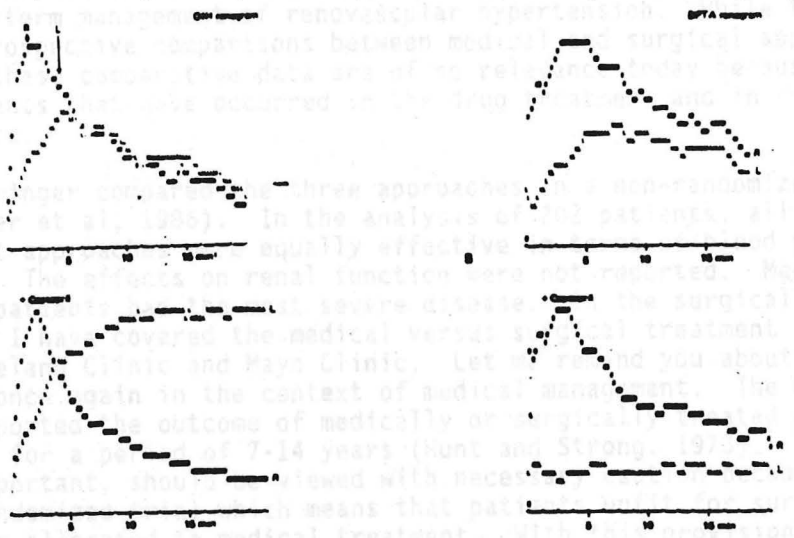


Figure 35: Renal plasma flow (ERPF), glomerular filtration rate (GFR), and blood pressure (BP) in four patients with severe bilateral stenosis studied during graded pressure reduction with nitroprusside before and after surgical revascularization. Preoperative study showed marked sensitivity to pressure reduction (left) that was no longer present after unilateral renal revascularization (right). Asterisk indicates $p < 0.05$, comparing preoperative and postoperative values at each period. (From Textor SC et al: Arch Intern Med 1985;143:2208-11).

Renal artery thrombosis has been reported to occur rarely following captopril therapy (Hoefnagels and Thien, 1986; Williams et al, 1984). This may have been related to regional fall in renal blood flow or due to systemic hypotension. Although useful in the management of patients with renovascular hypertension, ACE inhibitors should be used with caution. Renal function should be closely monitored. While this precaution can be implemented in patients with known renal artery stenosis, administration of ACE inhibitors in patients with undiagnosed renal artery stenosis poses certain amount of risk. Serum BUN and creatinine should be checked during the first week and periodically thereafter. Should the renal function decline, therapy should be stopped and the patient investigated for renovascular hypertension.

The ACE inhibitors and beta-blocking drugs by virtue of their mechanisms of action can be considered as rational choices for medical management of renovascular hypertension. However, (other) standard antihypertensive drugs can be used as long as the blood pressure control and renal function stability are maintained. Diuretics are often used in the treatment of hypertension but they do not offer any advantage over non-diuretic drugs in renovascular hypertension. Experimental and clinical studies have shown that diuretics are less efficacious in high renin hypertension. They may occasionally cause a paradoxical rise of blood pressure in high renin hypertension (Baer et al, 1977). In complicated hypertension, especially when renal insufficiency is present, loop diuretics complement other efforts to lower the blood pressure. Other drugs - prazosin (Curtis and Bateman, 1975), nifedipine (Bursztyn et al, 1985), hydralazine, and minoxidil can be used to control renovascular hypertension.

Figure 36: (From Geyes GG, Oei HY, Faber JAJ: Nephrol 1986;44(Suppl 1):54-9)



[A] Data of a man, age 56 years with hypertension, a normal serum creatinine concentration and a stenosis of the left renal artery. Blood pressure before PTA 240/130, after PTA 160/105. OIH renogram without (top) and during (bottom) captopril, both before PTA. Captopril has changed the curve of the left kidney.

[B] Patient as in to the left, also before PTA. DTPA renogram without (top) and during (bottom) captopril. During captopril the left kidney does not show any uptake of DTPA.

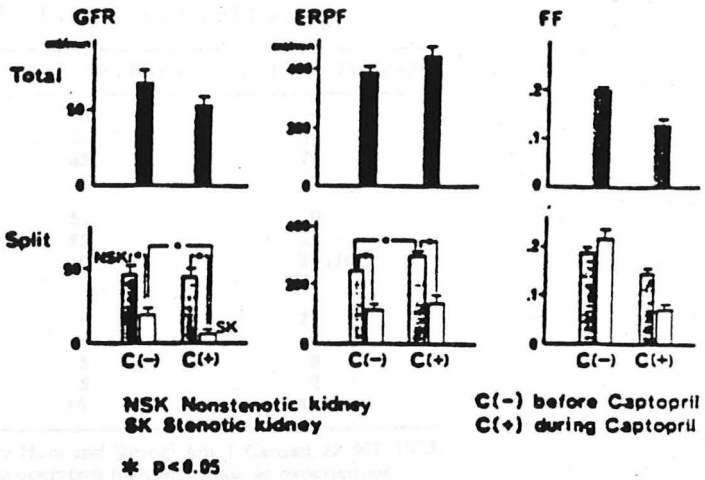


Figure 37: Effects of captopril on total and split renal function in 5 patients with renovascular hypertension with unilateral arterial stenosis. Glomerular filtration rate (GFR), but not effective renal plasma flow (ERPF), was significantly reduced in the stenotic kidneys (white bars). In the nonstenotic kidneys (gray bars) GFR was unaltered by captopril. (From Miyamori I et al: Hypertension 1986;8:415-21).

E. COMPARISON OF THERAPIES FOR RENOVASCULAR HYPERTENSION

There have been no randomized clinical trials comparing the efficacy of three therapeutic modalities - medical, surgical, PTRA - in the long-term management of renovascular hypertension. While there have been retrospective comparisons between medical and surgical approaches, many of these comparative data are of no relevance today because of great improvements that have occurred in the drug treatment and in surgical techniques.

Greminger compared the three approaches in a non-randomized fashion (Greminger et al, 1986). In the analysis of 202 patients, all the different approaches were equally effective in terms of blood pressure control. The effects on renal function were not reported. Medically treated patients had the most severe disease. In the surgical treatment section, I have covered the medical versus surgical treatment results from the Cleveland Clinic and Mayo Clinic. Let me remind you about these figures once again in the context of medical management. The Mayo Clinic group reported the outcome of medically or surgically treated patients followed for a period of 7-14 years (Hunt and Strong, 1973). The results, while important, should be viewed with necessary caution because it was not a randomized trial which means that patients unfit for surgery may have been allocated to medical treatment. With this provision, the surgical group fared much better than the medically treated group.

Table 43: Medical and Surgical Therapy Results on Renovascular Hypertension After 7- to 14-Year Follow-Up*

	SURGICAL THERAPY	MEDICAL THERAPY
Total Number of Patients	100	114
Atherosclerosis	37	44
Fibromuscular dysplasia	63	70
Blood Pressure Status of Living Patients		
Cured	51	0
Controlled	33	52
Uncontrolled	0	23 (16†)
Cause of Death During Follow-up		
Myocardial infarction	6	21
Stroke	4	8
Renal failure	3	8
Miscellaneous	3	2
Total	16	39

*Mayo Clinic Prospective Study. Adapted from Hunt and Strong: Am. J. Cardiol. *32*:562, 1973.
†16 medical-group patients were submitted to operation for uncontrollable hypertension.

In the Vanderbilt study, medically treated patients did poorly over the 28 month period (Dean et al, 1981). The disturbing observations were that renal function and size declined in a number of patients despite a satisfactory control of hypertension. It should be emphasized that these studies were conducted prior to the availability of ACE inhibitors and the new generation beta-blockers. In a more recent report from the Cleveland Clinic, the three treatment modalities were compared in 50 elderly patients (Olin et al, 1985). The surgically treated group had the best overall survival. Renal function deteriorated in over half of the medically treated patients. Not surprisingly, in this age group PTRA was successful in less than half of the patients treated by balloon dilation. A more recent analysis of the European experience (Zeck et al, 1986) shows the overall effectiveness of surgical treatment in 90% of the patients compared to 85% in the medical treated population. The cost-benefit analyses of different therapeutic modalities are shown in Tables 44 and 45.

Table 44: Cost-benefit analysis of three different types of treatment of renovascular hypertension due to fibromuscular dysplasia. (From Pickering TG et al: J Hypertens 1987 [In press]).

	Medical	Surgical	Angioplasty
Costs			
Financial	Low (but cumulative)	High	Moderate
Risk associated with treatment	Low (side effects)	Low	Low
Risks to renal function	20% deteriorate	Low	Low
Benefits			
Probability of cure	0	70%	70%
Probability of BP improvement	95%	25%	25%

Table 45: Cost-benefit analysis of three different types of treatment of renovascular hypertension due to atheroma (focal or diffuse). (From Pickering TG et al: J Hypertens 1987 [In Press]).

	Medical	Surgical	Angioplasty
Costs			
Financial	Low (but cumulative)	High	Moderate
Risks associated with treatment	Low (side effects)	Low (focal) Moderate-high (diffuse)	Low (focal) Low-moderate (diffuse)
Risks to renal function	50% deteriorate	Low	Low
Benefits			
Probability of cure	0%	40% (focal)	30% (focal)
Probability of BP improvement	95%	45% (focal) 45% (diffuse)	60% (focal)

At the present time, in the experienced centers the three therapeutic approaches yield excellent short-term results. Until valid data are reported concerning the ultimate role of PTRA it is not possible to provide a balanced judgement about the superiority of one technique over the other. Surgical treatment continues to provide the best long-term benefit but PTRA will be increasingly utilized in the treatment of renovascular hypertension. Long-term medical treatment is reserved for patients who are unsuitable for surgery or PTRA and for those who have failed to respond to these procedures.

XII. RENOVASCULAR HYPERTENSION IN SPECIAL SITUATIONS

A. RENOVASCULAR HYPERTENSION IN PATIENTS WITH RENAL INSUFFICIENCY OR COMPLETELY OCCLUDED RENAL ARTERY

Some patients with renal artery stenoses understandably present with renal insufficiency. The most common setting for this is bilateral renal vascular disease although it could also be seen in patients with renal artery stenosis of a solitary kidney. Recall that even in patients with unilateral renal artery stenosis, hypertension can damage the opposite kidney resulting in renal insufficiency. The question is whether revascularization or PTRA is helpful under such circumstances.

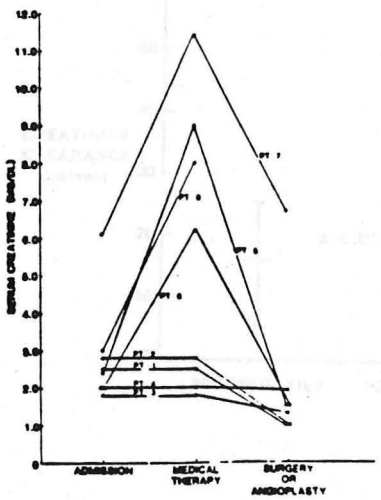


Figure 38: Effects of Medical Therapy and Surgery or Angioplasty on Serum Creatinine Levels. Serum creatinine values represent the averages of three or more determinations. Pt. denotes Patient. To convert milligrams per deciliter to micormoles per liter, multiply by 88.4. (From Ying CY et al: NEJM 1984;311:1070-5).

Studies indicate that refractory hypertension and renal insufficiency are not uncommon manifestations of renovascular hypertension. Expert surgical treatment produces an improvement in renal function together with better blood pressure control in these patients (Ying et al, 1984; Novick et al, 1983; Novick et al, 1984) (Figure 38). With careful medical and surgical efforts, many patients with renovascular hypertension and azotemia can be benefited substantially (Figures 39 and 40). Needless to say, such patients tend to have advanced atherosclerotic disease and are often sicker than uncomplicated unilateral renovascular hypertension.

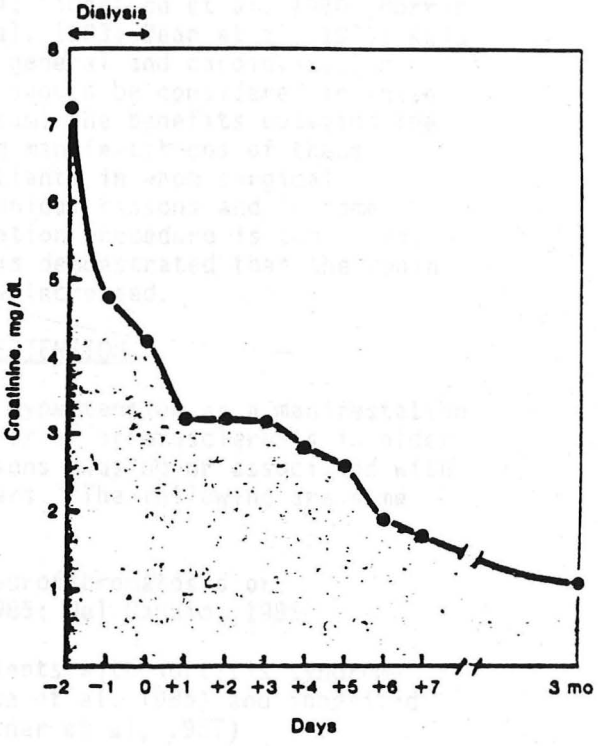


Figure 39: Improvement in renal function following successful renal revascularization in a patient with renal failure. (From Fry RE and Fry WJ: Arch Surg 1982;117:938-41).

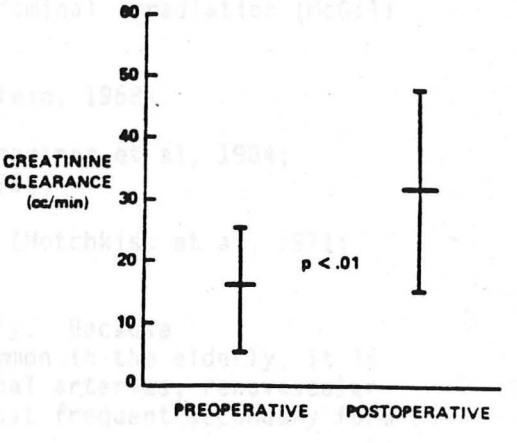


Figure 40: Changes in creatinine clearance after revascularization of 25 kidneys with preoperative creatinine clearance less than 30 ml/min. (From Dean and Rhamy: In: Stanley, Ernst, Fry, eds. Renovascular Hypertension. Philadelphia: W.B. Saunders, 1984:135-145).

B. SEVERE RENOVASCULAR DISEASE WITH TOTAL OCCLUSION OF THE RENAL ARTERY

Patients with completely occluded renal arteries with or without renal failure pose a challenging medical problem. The survival of these patients is determined by progression of vascular disease and a steady deterioration of renal function. Renal revascularization can be successfully done in properly selected patients with resultant improvement in blood pressure control, renal function, and even reversal of renal failure (Morgan et al, 1974; Dustan , 1984; Libertino et al, 1980; Morris et al, 1962; Textor et al, 1983; Luft et al, 1983; Dean et al, 1979; Raju and Williams, 1986). Unless the patients general and cardiovascular status is poor, revascularization or PTRA should be considered in these patients. With an experienced surgical team, the benefits outweigh the surgical risk despite the bleak presenting manifestations of these patients. Nephrectomy is reserved for patients in whom surgical revascularization is not possible for technical reasons and in some elderly patients in whom the revascularization procedure is too risky. Nephrectomy should only be done after it is demonstrated that the renin output from the stenotic kidney is clearly increased.

C. UNUSUAL FORMS OF RENOVASCULAR HYPERTENSION

Although we think of renovascular hypertension as a manifestation of fibromuscular dysplasia in young women or of atherosclerosis in older women, the spectrum of renal arterial lesions causing or associated with hypertension reflects a variety of disorders. The following are some examples:

1) Renovascular hypertension with neurofibromatosis or pheochromocytoma (Elias et al, 1985; Del Gaudio, 1985)

2) Renovascular hypertension in patients with aortitis syndrome (Lagneau and Michel, 1985; Morooka et al, 1985) and inherited vascular collagen disorders (Luscher et al, 1987)

3) Renovascular hypertension with renal artery aneurysms (Than et al, 1983; Stanley et al, 1975)

4) Renovascular hypertension following abdominal irradiation (McGill et al, 1979, Salvi et al, 1983)

5) Segmental renal artery stenosis (Bookstein, 1968)

6) Renal transplant artery stenosis (Baumgartner et al, 1984; Dickerman et al, 1980; Khoury et al, 1983)

7) Renovascular hypertension in pregnancy (Hotchkiss et al, 1971; Sellars et al, 1985)

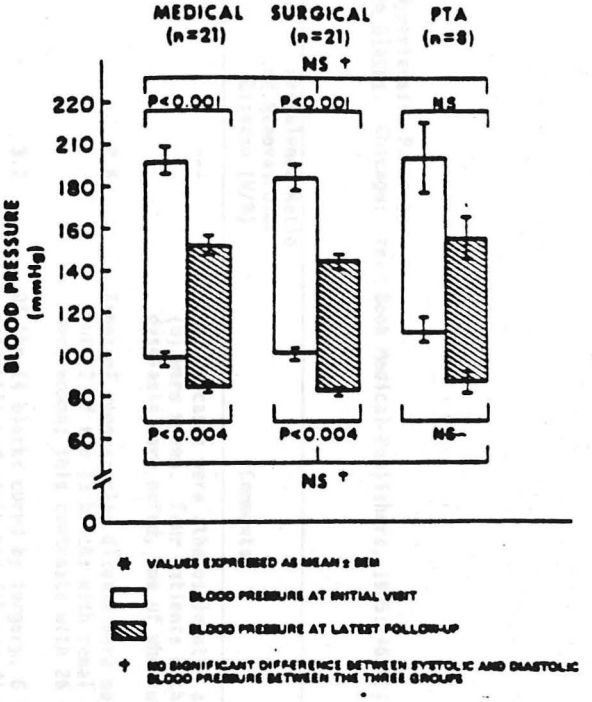
8) Renovascular hypertension in the elderly. Because atherosclerotic vascular disease is common in the elderly, it is not surprising that when it affects renal arteries, renovascular hypertension may develop. It is the most frequent secondary form

of hypertension identified in the elderly. The therapeutic decision must be weighed against a number of physiological and pathophysiological factors governing the proper approach to elderly patients with renal artery stenosis. In patients with stable renal function and reasonable control of hypertension, long-term medical therapy is implemented. However, age alone should not ruled out surgical option if an operation is indicated by the status of hypertension and/or renal function.

Table 46: Results of Surgical Treatment According to Age (From Dean RH and Foster JH: Med Clin N Amer 1977;61:643-53).

	50–54	55–59	60–65	65+
Cure	5	16	5	2
Improved	16	14	6	3
Failure	1	6	3	—

Figure 41: Blood pressure at initial visit and latest follow-up study. PTA = percutaneous transluminal angioplasty. (From Olin JW et al: JACC 1985;5:1232-8).



The presence of heart and cerebrovascular disease increase the surgical risk and restrict the long-term benefits expected of revascularization. Obvious criteria useful in helping identify renovascular hypertension in the elderly are sudden onset of hypertension

Table 47: Prevalence of Renovascular Hypertension in Black (B) and White (W) Hypertensive Patients (Modified from Hall WD, Saunders E, Shulman NB, eds. Hypertension in Blacks. Chicago: Year Book Medical Publishers, 1985:146-4.)

Author(s)	Definition of Renovascular Disease	No. Patients With Hypertension	No. Patients With Renovascular Disease (%)	Prevalence Ratio of Renovascular Disease (W/B)	Comments
Thomas et al, 1965	Positive arteriogram	B: 100 W: ---	B: 16 (16%) W: --	---	12 of 16 cases were atherosclerotic and most (8) were women. Four patients with fibrous dysplasia were noted, one of whom was male.
Foster et al, 1966	Arteriogram with stenosis of one or more renal arteries	B: 81 W: 127	B: 13 (16.0%) W: 53 (41.7%)	2.6	Types of renovascular disease were not specified, but 12 of the 13 blacks with renal artery disease were women; this contrasts with 26 of the 53 whites.
Simon et al, 1972	Patients with positive arteriograms who were subsequently operated on and cured	B: 112 W: 404	B: 14 (12.5%) W: 161 (39.9%)	3.2	Of the 14 blacks cured by surgery, 6 had atherosclerotic and eigth had fibrous disease. The corresponding numbers in whites were 85 and 78, respectively.
Grim et al, 1979	Arteriogram with stenosis plus a renal vein renin ratio consistent with the diagnosis	B: 87 W: 377	B: 0 (0%) W: 44 (11.7%)	>6	Renal arteriograms were performed in 279 of the 464 hypertensive patients.
Davis et al, 1979	Arteriogram with more than 25% atherosclerotic narrowing of renal artery, or with fibromuscular dysplasia	B: 29 W: 56	B: 2 (6.9%) W: 24 (42.9%)	6.2	Accelerated or malignant hypertension was defined as a diastolic blood pressure of 125 mm Hg or more plus funduscopic hemorrhages, exudates, or papilledema.
Keith et al, 1982	Arteriogram with 50% or greater narrowing of the renal artery of one of its primary branches	B: 7,200 W: ---	B: 47 (0.65%) W: --	---	32 cases (10 men and 22 women) were atherosclerotic; 11 (9 women and 2 men) were fibrous dysplasia; 4 were due to miscellaneous causes such as thrombosis.

or rapid deterioration in blood pressure control and or renal function. Operative treatment or PTRA should be considered in patients who pose difficulties in management with drug therapy. With proper peri-operative care, good surgical outcome can be expected in properly selected elderly patients (Olin et al, 1985; Dean and Foster, 1977) (Figure 41). In patients with significantly coronary or carotid disease, these conditions should be corrected first before planning renovascular repair. Experience with PTRA is limited in elderly patients with renal artery stenosis. Which ever therapy is chosen, these patients need careful evaluation and close follow-up.

RENOVASCULAR HYPERTENSION IN BLACK PATIENTS

Hypertension is common among black patients and cause considerable mortality in this group. Since blacks are at a greater risk for hypertension induced sequelae, identification of secondary forms including renovascular hypertension deserves consideration. Although it is generally believed that renovascular hypertension is rare in blacks, there have been no systematic efforts to determine the precise incidence of remediable forms of hypertension in the blacks. The relative rarity of renovascular hypertension has been emphasized by a number of investigators.

In the Co-operative Study, only 8% of the patients with renal artery stenosis were black, although blacks constituted 30% of the entire study sample. Similarly, Keith noted only 47 cases of renovascular hypertension in 7200 black hypertensive patients undergoing evaluation (Keith, 1982). The low statistical incidence should be viewed with the knowledge that renal arteriography was performed in only 238 patients. So the true incidence, however small it may be, can not be calculated from this study. Grimm and co-workers did not find a single instance of functional renal artery stenosis in 87 hypertensive blacks subjected to extensive evaluation (Grimm et al, 1979). But Foster and associates detected renal artery stenosis in 13 of 81 hypertensive blacks receiving special diagnostic evaluation (Foster et al, 1966). These divergent figures possibly reflect different referral patterns. In accelerated or malignant hypertension, renal artery stenosis was found in 2 of 29 blacks, compared to 24 of 56 whites (Davis et al, 1979). Table 47 shows the incidence of renovascular hypertension in blacks from different series. The treatment of renovascular hypertension in blacks is similar to whites. It is not known whether ACE inhibitors are effective in the medical management of blacks with renovascular hypertension. It is of historical curiosity that the first surgical cure of renovascular hypertension was recorded in a black child (Leadbetter and Burkland, 1938).

RENOVASCULAR HYPERTENSION IN CHILDREN

Next to aortic coarctation, renal artery stenosis is the most common correctable form of hypertension in children. The detection of renovascular hypertension in childhood varies from one institution to another. A high prevalence of 23% was reported from one specialized center (Singh and Page, 1967). The true prevalence is not known. Loggie estimated that renal artery stenosis accounted for 5% of all children with hypertension at the University of Cincinnati (Loggie, 1985).

The developmental vascular abnormalities and fibrous dysplasia are the most common types of renal artery stenosis in children. In some parts of the world, aortitis syndromes are the major cause of renovascular hypertension in the young (Sharma et al, 1985).

Renovascular hypertension in children can be very severe and refractory to treatment. The implications of long-term drug therapy in this age group remain unknown. With meticulous preoperative evaluation and surgical techniques, excellent results have been reported (Fry, 1985; Fry, 1973).

XIII. THE SPECTRUM OF RENOVASCULAR HYPERTENSION - ILLUSTRATIVE CASES

Case 1: Renovasclar hypertension in a patient with severe hypertension.

J.M., a 46 year old white female was admitted to the hospital because of chronic hypertension which has not responded to incremental doses of antihypertensive drugs. The patient's blood pressure was 210/140 mm Hg on hydralazine (200 mg/day), metoprolol (200 mg/day) and furosemide (80 mg/day). As the doses were gradually doubled, blood pressure stabilized at 170/106 mm Hg.

The possibility of renovascular hypertension was considered based on the above clinical course plus the presence of a high pitched systolic-diastolic abdominal bruit and the work-up revealed bilateral atherosclerotic renal artery stenosis. Renal vein renins were 85 ng/ml/hr (left) and 18 ng/ml/hr (right), vena caval PRA was 20 ng/ml/hr. The renal vein renin ratio--left:right was 4.7:1 and surgery was recommended. The night before surgery her blood pressure remained at 200/110. A few days after surgery, her blood pressure stabilized close to 130/90 (off treatment). Subsequent follow-up in the office revealed blood pressures 140-150/90 but her home blood pressures were much lower--130-80.

This case underscores the need to consider renovascular hypertension in a patient not responding to potent antihypertensive drugs.

Case 2: Renovascular hypertension in the patient with abrupt onset of hypertension.

L.A., a 65 year old white male, was seen because of hypertension which was detected when the patient was admitted to another hospital with stroke. Fortunately, he recovered from the stroke (hemorrhage) without any deficits. This patient was under the medical supervision of his family doctor for many years and his blood pressure was "normal" until the above event. Patient continued to have hypertension following discharge. His blood pressures in the office were 190/116-208/120 (on diuretics). In view of the rather abrupt and new onset of hypertension, a digital angiogram was done which revealed left renal artery stenosis (atherosclerotic). The renal vein renins were as follows--left 73 ng/ml/hr, right 21 ng/ml/hr and peripheral PRA was 28. PTRA was done following which his blood pressure improved substantially (130-140/80).

This case illustrates the classical abrupt onset of hypertension in an elderly patient with underlying renal artery stenosis.

Case 3: Renovascular hypertension cured by unilateral nephrectomy.

D.M., a 51 year old male was evaluated because of severe hypertension (BP 210/140 on multiple drugs). The blood pressure responded fairly well to minoxidil, beta-blockers and diuretics but the patient developed congestive heart failure posing considerable therapeutic problems. The patient had undergone surgery for right renal artery stenosis many years ago.

A re-evaluation for renovascular hypertension revealed near total occlusion of the right renal artery. Renal vein renins were 41 ng/ml/hr (right), 10 ng/ml/hr (left) and peripheral PRA was 31 ng/ml/hr. Therefore, this patient had contralateral suppression of renal vein renin (ratio 4:1), further indicating the pathogenetic role of the right kidney. Surgery was recommended due to problems with medical control. Due to technical difficulties, bypass was impossible and a right nephrectomy was done. Following this, the patient's course was uneventful with normalization of blood pressure without drug therapy.

This case illustrates the importance of surgical skill in deciding the type of operative approach in a patient with renal artery lesion that cannot be bypassed. Without proper judgment, unnecessary nephrectomies may result and on the same token in some patients like DM, anything short of nephrectomy would not have helped.

Case 4: PTRA may not have a lasting effect in some patients.

M.C., a 74 year old female was referred by her family physician because of increasing blood pressure despite good therapy. Her blood pressure was 200/108-110 on hydralazine (200 mg/day), propranolol (160 mg/day) and HCT (50 mg/day). She had a loud high-pitched abdominal bruit. IVP was normal but in view of severe hypertension, an arteriogram was done which revealed right renal artery stenosis. The renal vein renin ratio was nearly 2:1 (right to left). PTRA was performed which improved the blood pressure to 150/80 (on therapy) in the hospital. Follow-up for the next 6 months demonstrated a progressive rise in blood pressure to pre-PTRA levels despite drug therapy.

The above case illustrated the need for careful follow-up of patients undergoing balloon dilatation.

Case 5: Failure of surgery to correct hypertension in a patient with non-lateralizing renin secretion.

H.T., a 57 year old female with a history of hypertension (unknown duration) was evaluated because of a mild stroke from hypertension. The blood pressures ranged close to 170/100 on therapy. Sequential investigations showed right renal artery stenosis (fibromuscular hyperplasia). The renal vein renins were 5.8 and 4.6 ng/ml/hr in the right and left, respectively. A few months later surgery was performed to correct the stenosis. The blood pressure did not fall and 6 weeks later

it was 170/100 (on medication). The blood pressure continued to remain high requiring multiple drugs. The above case illustrates that surgical success cannot be predicted if the stenotic kidney does not demonstrate hypersecretion of renin. However, there are many exceptions to this phenomenon.

XIV. SUMMARY

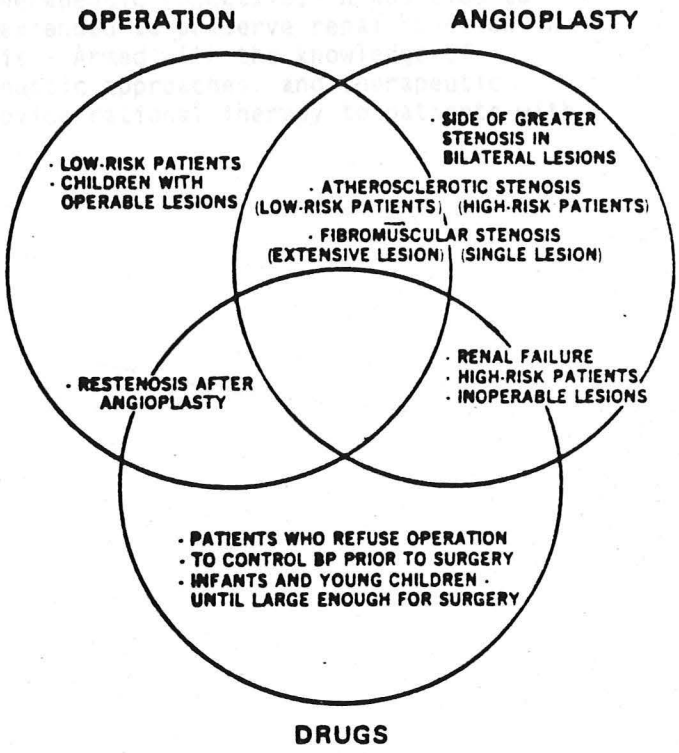
Having reviewed such an abundance of information, we require some overview that might be of value in gaining an overall perspective of clinical renovascular hypertension. The staggering body of evolving concepts and of established facts signifies the implications of renal arterial occlusion in patients with hypertension. As we enter a period of scientific renaissance many gaps in our knowledge will likely be bridged.

Renovascular hypertension is the most prevalent form of curable hypertension. Despite some unanswered questions, there is growing consensus about the need to identify patients with renovascular hypertension so that specific therapy can be recommended. The renin-angiotensin system is the chief pathophysiological mechanism responsible for hypertension in patients with renal ischemia but other yet poorly defined mechanisms may be operative. Most patients with renovascular hypertension do not present with typical or discriminative clinical features and are indistinguishable from patients with essential hypertension. Thus, many physicians do not perform work-up to uncover renovascular disease even if diagnosis is dictated by patients' clinical course. It is difficult to make the proper diagnosis unless there is a high index of suspicion and certain procedures are performed. How can we, then select a few patients for the work-up from the vast sea of people with hypertension? The identification of such patients and the pursuit of a renovascular etiology is a matter of clinical judgement. Delineation of renovascular hypertension should be undertaken only after careful deliberation. When clinical clues suggestive of renovascular hypertension are present, appropriate diagnostic tests should be undertaken in patients who are candidates for PTRA or surgery. Captopril stimulated PRA test is done first. If the test is positive (and in some clinically relevant circumstances even if it is not done or negative), DSA should be obtained. IV-DSA is being steadily replaced by the superior IA-DSA. The need for renal vein renin determination varies from center to center but when carefully performed, it yields meaningful information. Ultimately a conventional arteriogram is done to define the extent of renal artery stenosis and to assess intrarenal vascular anatomy.

The resources should be sent tactfully to avoid indiscriminate and unnecessary work-up. This notion should especially be appreciated in the present climate of Diagnosis Related Groups and other cost-containment measures. For selected patients, the benefit-risk ratio clearly outweighs the cost considerations. The spectrum of renovascular hypertension is variable, further compounding the diagnostic indications and contraindications. At one end of this spectrum are those patients in whom surgical therapy is likely to be beneficial and at the other end are the patients who have relative contraindications for surgery. In between lies the vast gray zone which constitutes a great judgemental challenge in clinical medicine. What to do with the patients who have mild to moderate

renovascular hypertension whose blood pressure is controlled on medical therapy? The three therapeutic choices are not mutually exclusive. Based on patient's clinical course, the therapeutic option can be shifted from one modality to another.

Figure 42: Therapeutic strategies for patients with renovascular hypertension. (From Maxwell MH: Practical Cardiol 1987, May).



There are some patients who may benefit from renovascular repair despite the non-lateralization of renal vein renins. What is the mechanism underlying their hypertension? In medically treated patients, surgery or angioplasty must be considered when the blood pressure is poorly controlled, when the renal function is getting worse, and when the patient compliance is not optimal. Thus, the therapeutic decisions made at one time may be subject to revisions at a later time.

There is no doubt that our ability to treat renovascular hypertension with drugs, with surgical techniques and with PTRA has improved a great deal. These modalities are not mutually exclusive. The PTRA has added another dimension to the management of renovascular hypertension. Since the public and professional awareness of hypertension is steadily growing, one can anticipate an increasing number of patients with renovascular hypertension. And, the developing trends in the radiological technologies will aid the physician in uncovering more patients with renovascular hypertension. The availability of experienced vascular surgeons and

angiographers is of paramount importance in the ultimate benefit to be derived by the patient. In the last few years we have witnessed elucidation of the renin system, the role of kidney in sustaining high blood pressure under the conditions of renal ischemia, and have gained knowledge about the natural course of renal arterial occlusive disease.

Finally, the therapeutic options for treating renovascular hypertension have widened. The therapeutic objective, in addition to blood pressure control, has been extended to preserve renal function in patients with renal artery stenosis. Armed with the knowledge of pathophysiological concepts, diagnostic approaches, and therapeutic modalities, we are now able to provide rational therapy to patients with renal artery stenosis.

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