RATIONALE AND USE OF VASODILATED EXCRETORY UROGRAPHY IN SCREENING FOR RENOVASCULAR HYPERTENSION*

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OVER the last few years there has been a dramatic increase in medical concern about the diagnosis and treatment of hypertension. The Veterans Administration Cooperative Studies[31,32] have convincingly demonstrated the potential benefits to be realized by effective antihypertensive treatments. However, clinical investigations continue to reveal subgroups of hypertensives for whom unique therapies may be indicated; *i.e.*, propanolol for high renin essential hypertension,[2] spironolactone for low renin essential hypertension,[4] and surgery for renovascular hypertension.[19] Sophisticated diagnostic tests are frequently necessary to cull these subgroups from among the millions of known hypertensives. There may be as many as 5 million hypertensives in the United States alone who have surgically curable secondary hypertension.

Were dollars and diagnostic resources unlimited, each hypertensive might reasonably be given an extensive diagnostic evaluation. This is an unattainable objective in that the number of hypertensives may approach 20–30 million Americans. Screening tests must of necessity be employed. Since the evidence suggests it is the lowering of blood pressure that is beneficial, why not use medical therapy for screening and work-up the medical failures? Due to the large numbers of patients involved, this approach has much to recommend it. However, life-long drug treatment of an essentially asymptomatic disease is quite difficult to achieve and not inexpensive. To the extent that medical therapy is ineffective, patients with surgically curable hypertension are subject to needless risk.

In his role as a diagnostic consultant, the radiologist most frequently faces this uncertain situation in the form of a request for a "hypertensive IVP." It is safe to assume that the referring physician wishes to know if the patient has renal hypertension. There are many forms of renal disease responsible for hypertension.[9] The anatomic information available from an excretory urogram frequently provides important information in the differential diagnosis. However, an examination with even minor risk should not be performed unless the result could influence therapy for the patient. The ideal screening test for renovascular hypertension must identify patients who do not have surgically correctable renovascular hypertension as well as those who may.

We have previously reported, in preliminary form,[36] that Vasodilated Excretory Urography (VEU) provided a more accurate reflection of the true renal hemodynamic state than the hypertensive intravenous pyelogram (IVP). The purpose of this report is to extend those observations and to discuss the renal physiology which makes VEU the best screening test presently available.

INFORMATION AVAILABLE FROM EXCRETORY UROGRAPHY

The presence of a significant renal hemodynamic defect is suspected during excretory urography from either a difference in

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renal size or a disparity in contrast medium excretion. Renal length is usually measured on the preliminary film (the least discriminant in the entire study), but may be measured at any time. On the other hand, contrast medium excretion is considered to be a variable, where timing is crucial.[21] Actually both renal size and contrast medium excretion are physiologic variables. Before diagnostic significance can be accorded either, one should understand the physiologic basis for the "standard ideas" of delayed appearance, delayed hyperconcentration, spidering, etc.

Disparity in pelvocalyceal opacification following bolus injections of contrast media and positive split function tests are assumed to result from excessive reabsorption of water in the affected kidney.[10,21,27] Since diatrizoate and iothalamate salts are, for the purposes of rapid-sequence urography, distributed and excreted like inulin,[24] it is tempting to believe that contrast media excretions may provide the same information as inulin concentration in split function testing.

There are several reasons for suggesting that the physiologic processes at work during bolus excretory urography may be more complex. First, split function tests are performed under clearance conditions, and renal physiologists have vigorous objections to interpreting any renal clearances obtained under rapidly changing circumstances.[34] Most pertinent to the conditions of excretory urography is the normal heterogeneity of nephron lengths. Short nephrons will excrete substances such as inulin and contrast material more quickly than long nephrons. The magnitude of this phenomenon, known as nephron delay time, can be appreciated following bolus injection of inulin in normal man. Only 1 per cent of the resulting immediate glomerular filtrate reaches the bladder in 1 minute. Longer nephrons are slower, so that 21 per cent of the initial filtrate requires 4 minutes to reach the bladder.[5] For contrast media, the phenomenon is clearly revealed in that peak excreted contrast concentrations are reached at 15–30 minutes, whereas the peak filtered concentrations are achieved within the first circulation time.[8,17] Thus the earliest opacification of the pelvocalyceal system is accomplished by only a fraction of the nephrons of that kidney. The only effective compensation for nephron delay is constant plasma concentration so that each filtered volume starts with the same composition. The influence of hemodynamic factors in nephron delay time is unknown.

A second important difference exists between measured inulin concentrations and subjective estimates of pelvocalyceal opacification. Significant differences in inulin concentration range from 100–500 per cent.[27] Density of pelvocalyceal opacification depends upon the amount (volume times concentration), rather than concentration alone.[8] In addition, 2–4 fold differences in urine concentrations of contrast material may be impossible to distinguish at urography.[22]

Thirdly, mannitol, an osmotic diuretic, tends to eliminate the differences in inulin concentrations in positive split function tests.[27] The contrast agents are very similar to mannitol in their hemodynamic and diuretic effects upon the kidney.

The physiologic conditions are considerably more stable in the later films of the study when plasma concentrations of contrast media are falling less rapidly and the stressful stimuli attending the bolus injection have waned. One might expect delayed hyperconcentration to reflect the excessive tubular reabsorption caused by a significant stenosis. In fact, delayed hyperconcentration is considerably less discriminant than delayed appearance time.[1,20]

In view of these considerations, one wonders how a disparity in contrast medium excretion can ever accurately reflect the hemodynamic lesion. Yet, contrast disparities do indicate the presence or absence of significant stenosis with an accuracy well beyond chance expectations. It seems possible that the vasodilator properties of intravenous contrast agents enhance the

excretion rate from the kidney with normal vasodilator reserve and are not as effectively diuretic in the presence of significant stenosis. Earley and Friedler[11] have shown that vasodilator diuresis due to acetylcholine can be significantly diminished by aortic coarctation.

MATERIAL AND METHOD

This report is based on 250 VEUs performed on hypertensive patients referred to the Radiology Department for a "hypertensive IVP." They were routinely prepared for urography by overnight dehydration, cathartics, and clear liquid diet. Following the preliminary roentgenogram, 50 ml. of conray 400* was injected into the antecubital vein within 20–30 seconds. Subsequent roentgenograms were taken at 1, 2, 3, 5, 8, and 15 minutes. Following the 3 minute film, 50 mg. of ethacrynic acid (edecrin, Merck Sharp and Dohme) was injected intravenously over a period of 1–2 minutes. About one-third of the patients noted pain at the injection site, probably due to the low pH of the diuretic solution. The painful response lasted less than 2 minutes. Because of the rapid diuresis after ethacrynic acid (ECA), it was found necessary to infuse a solution of 50 ml. conray 400 in 200 ml. of saline by intravenous drip to maintain renal silhouette visibility. Renal silhouettes, using the medial tangent method,[14] were outlined with a wax pencil directly on the resulting roentgenograms and their areas determined with a compensating polar planimeter.

RESULTS

1. MEASUREMENTS OF RENAL SIZE

The first prerequisite for performing an experiment is to determine if the parameters of interest can be reproducibly measured. Many radiologists are dubious that renal size changes of the order reported here can be accurately detected. On the contrary, when the renal silhouettes are visible, very accurate measurements can be made. Thus, Klatte *et al.*[20] estimated an error in length of 1.2 per cent and width 2.4 per cent on independent measurements by 3 observers. Vuorinen and Wegelius[33] achieved a highly significant difference in renal length times width before and after mild osmotic diuresis (glucose) when the average difference was only 2.4 cm.^{2}, or about 3 per cent.

Actual measurement of silhouette area is inherently more accurate than length times width because of the marked increase in the number of decision points. The correlation between silhouette area, length, width, and length times width for 40 roentgenograms is shown in Table 1. Of course, no method can accurately measure poorly defined silhouettes. The earliest film following contrast medium injection had to be used for minimum size in 41 kidneys in the 250 studies because preliminary renal shadows could not be identified with confidence, even in retrospect.

2. THE NORMAL RESPONSE

Figure 1 reflects the time course of a typical VEU response in a hypertensive patient with a normal arteriogram and no lateralization of renins. The transient decrease in renal size with the painful response to ECA is seen at 5 minutes. The normalized response for 200 patients with the presumptive diagnosis of essential hypertension is depicted in Figure 2. The 2, 5 (no pain), and 15 minute areas are all different from the preliminary area ($p < .001$).

Any agent that effectively decreases renal resistance without causing systemic pressure (the distending force) to fall

TABLE I

CORRELATION OF SILHOUETTE AREA WITH LINEAR MEASUREMENTS OF RENAL SIZE

	Correlation Coefficient		
	Length	Width	Length×Width
Area	.65	.51	.83

* Sodium iothalamate, Mallinckrodt Pharmaceuticals, St. Louis, Missouri.

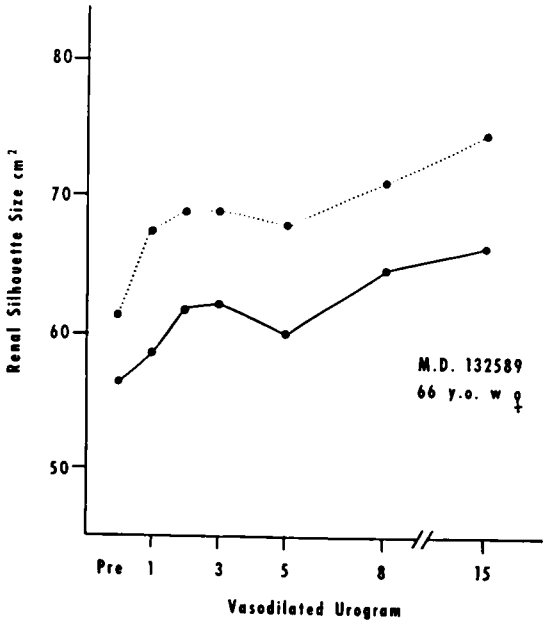

FIG. 1. Typical size changes during the vasodilated excretory urography (VEU) protocol in a hypertensive patient with no arterial stenosis. Right renal response is represented by the solid line, left renal response by the dotted line.

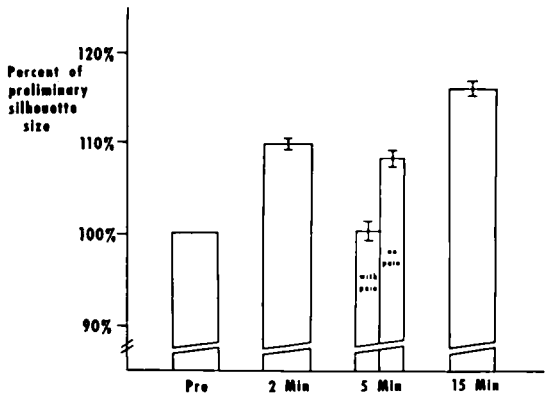

FIG. 2. Average response in 200 hypertensive patients with essential hypertension. The preliminary renal size is normalized to equal 100 per cent. Each bar represents the mean per cent of preliminary size ± 2 S.E.M.

would cause renal size to increase. The response to ECA is not specific since the average size increase with contrast agents is highly significant. However, our experience with the early renal swelling associated with the contrast bolus shows it to be diagnostically less reliable than the more potent and longer lasting ECA response. Nausea, pain, cardiovascular changes, and psychic stress appear to cause the unchanged or even decreased renal sizes seen in 10–15 per cent of the early films.

In the absence of these stimuli, renal size increases an average of about 10 per cent the first 2 minutes. When delineation of renal shadows is inadequate on the preliminary film, the earliest possible adequate nephrogram should be used instead. For the reasons above, one must accept the possibility of a spurious baseline reading, but, on the *average*, the following corrections can be used: 30 seconds– 2 per cent; 1 minute—5 per cent. Not infrequently, maximal vasodilatation is realized with contrast media and the 15 minute silhouettes are not much larger than at 2 minutes.

We consider that a size increase (maximum/preliminary × 100) greater than 10 per cent reflects adequate vasodilator reserve and, therefore, normal renal hemodynamics. The validity of this result is shown in Tables II and III. A positive arteriogram is defined as the presence of an anatomic stenosis measuring 30 per cent or greater. A significant stenosis would require lateralization of renins (ratio of 1.4 or

TABLE II

PER CENT AREA INCREASE VERSUS LENGTH AND CONTRAST DISPARITY FOR 250 EXAMINATIONS*

Area Increase (individual kidneys)	Length Difference (examinations)	Contrast Disparity (examinations)	Positive Arteriogram (individual kidneys)	Renin Lateralization (examinations)
1. Greater than 10 per cent n=415/489	12/250	8/250	4/72	0/42
2. Less than 5 per cent n=37/489	14/33	10/33	18/22	16/18

* Size increases not measurable for 11 kidneys; 37 kidneys increased 5–10 per cent. See text for further detail.

TABLE III

ACCURACY OF DIAGNOSTIC PREDICTION OF SIGNIFICANT STENOSIS BASED ON PER CENT SIZE INCREASE

	True	False Positive	False Negative
1. Normal VEU	72/72	—	0
2. Suspicious VEU	16/18	2/18	—

greater) in addition to the anatomic stenosis. Minor urographic signs were not included in this assessment. As evident in Table II, 4 kidneys had a normal size increase in the presence of stenosis that did not result in lateralization of renins.

In this series, size increases of 5–10 per cent were measured in 37 kidneys. For 32 of these, renal size was not assessable on the preliminary film. The uncertainties of preliminary size make these responses nondiagnostic. For the remaining 5 kidneys, 3 had roentgenographic evidence of pyelonephritis and 1 patient had biopsy-proven diabetic glomerulosclerosis.

3. PATIENTS WITH SIGNIFICANT STENOSIS

Table II shows that 37 kidneys failed to increase by 5 per cent. Arteriography and selective renins were obtained in 20 of the original 33 patients. Accuracy assessments are based on these 20 patients. Length differences were measured on the preliminary film. The methods included a shortened rapid-sequence protocol, and contrast disparities were assessed only on the films prior to ECA since the influence of this loop diuretic on contrast medium washout in the presence of significant stenosis is unknown. Thus the accuracy comparison of VEU *versus* rapid-sequence is not completely fair to the proponents of the latter.

The typical responses seen for patients with unilateral stenosis or bilateral stenosis are demonstrated in Figures 3 and 4, respectively. None of the 4 patients with bilateral blunted responses were detectable by urographic criteria. Only 2 patients were studied by arteriography and their renins did not lateralize.

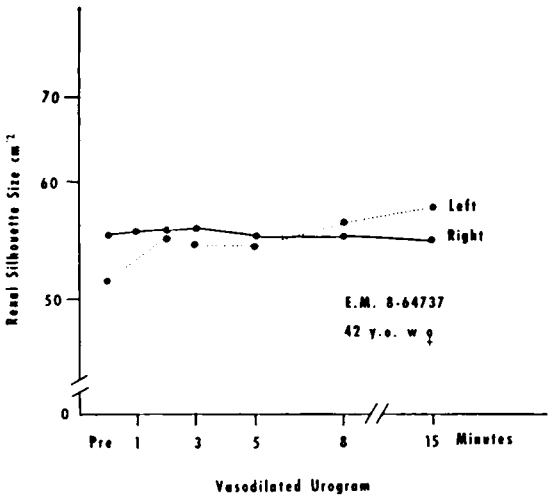

FIG. 3. The VEU response in a case with left fibromuscular dysplasia. Previous work-up includes 3 normal IVPs and 3 normal split function tests. She is markedly improved 8 months after renal by-pass grafting.

It is difficult to know what criteria to use as a standard of comparison to determine the "accuracy" of the diagnosis short of surgical cure. All 4 patients with unilateral stenosis treated surgically have had an excellent response, although the average follow-up is less than a year. The agreement of VEU with arteriography and selective renal vein renin ratios for unilateral stenosis only is as follows:

a. In 14 patients all 3 diagnostic modalities indicated the presence of a significant stenosis.
b. Twice, the abnormal VEU was associ-

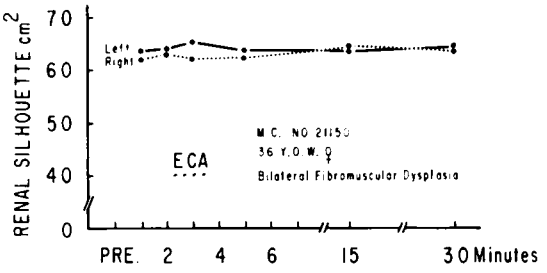

FIG. 4. The VEU response seen with bilateral significant stenosis. The patient had had 2 negative IVPs before this study led to confirmatory arteriography.

ated with normal renin and arteriographic studies.

c. On 2 occasions, the arteriogram was normal but renins lateralized to the side predicted by the VEU.

For the latter, small vessel disease would explain the apparently normal arteriogram. Including these 2 studies as true positives in Table III is debatable, since biopsy confirmation has not been possible. For all patients, the agreement of VEU predictions with other tests performed in the same patient is depicted in Figure 5.

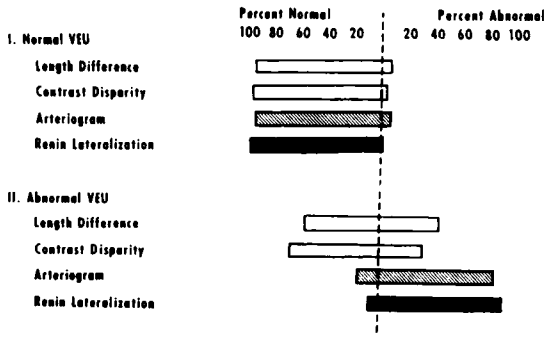

FIG. 5. Concordance of diagnostic tests with normal and abnormal VEU. This is a graphical summary of the data from Table II. Note that the predictions from dynamic changes in renal size are in much better agreement with the abnormal arteriograms and selective renal vein renins than are length difference or contrast disparity.

4. THE MECHANISM OF THE RESPONSE

In our preliminary report, we speculated that local regulatory mechanisms might decrease renal resistance as a compensatory response to renal arterial stenosis. The concept that a vasodilator reserve characteristic for each organ determines the degree of stenosis that is significant for the organ has been considered elsewhere.[35] Since vasodilator reserve is minimal for the kidney, stenoses near 50 per cent suffice to reduce resting renal blood flow, whereas 95 per cent stenosis may be required for skeletal muscle arteries.

In a series of dog experiments, we have examined the correlation of several renal parameters with renal size, either with or without induced renal arterial stenosis. These results can be summarized as follows:

a. The intravenous administration of clinical doses of contrast media causes a decrease in measured renal resistance of approximately 25 per cent in nembutal anesthetized dogs. The characteristic renal vasoconstriction seen with arteriographic doses is not demonstrated.[3] Infusions of contrast material into the renal artery cause renal vasodilatation throughout infusions lasting as long as 15 minutes.

b. Clinical doses of contrast media and ethacrynic acid increase renal size, subcapsular pressure[15] and urine volume, without significantly affecting glomerular filtration rate.

c. Increasing vascular stenosis progressively decreases vasodilator response by the kidney. As dilator reserve is lost, the usual increase in renal size is proportionately attenuated, the subcapsular pressure rise with contrast media and ethacrynic acid is markedly diminished, and diuretic response to either agent is blunted.

DISCUSSION

The results of our clinical and laboratory work support the investigations of Swann who first commented upon the "erectile" nature of the kidney.[6,29,30] The kidney is composed of 3 very distensible compartments: vascular, tubular, and interstitial. The relative pressure within each compartment strongly determines its volume. The distending pressure comes from the systemic circulation, while the several resistances in the kidney determine the extent to which any given distending pressure is transmitted. These resistances are subject to nervous, humoral, drug, and local regulatory influences and thus renal size is a dynamic variable.

The observations that renal size reflects the state of renal vessels can be traced to Starling.[28] Any stimulus that causes hypotension or a strong sympathetic discharge raising renal resistance can be expected to

cause rapid decreases that can be as large as 40–50 per cent.[6,18,26] The rapid decrease in renal size in response to pain reflects the characteristic increase in renal resistance seen in the so-called "defense reaction."[12]

Increases in renal size have generally been recorded with agents that cause renal vasodilatation and/or diuresis.[25,26,33,36,37] Vuorinen and Wegelius[33] appear to have first suggested that drugs might induce changes in renal size. Whether local vasodilatation associated with inflammatory processes or transplant rejection explains the transient increases in renal size seen with the oliguria of the glomerulonephrides, acute tubular necrosis, or transplant rejections[34] remains to be seen.

Our clinical application of induced changes in renal size is critically dependent upon those changes being large enough for accurate detection and their dependence upon hemodynamic events that occur principally on the arterial side. Actual measurement of renal volume[16] may be more sensitive than the silhouette area described herein. However, for screening purposes, satisfactory accuracy seems possible from single plane estimates of renal size.

The concepts of vasodilator reserve deserve more consideration in evaluating the significance of arterial pathology, since a functional rather than anatomic interpretation is obtained. By applying these precepts, the significant anatomic stenosis for the kidney is approximately 50 per cent. It is also at this level that the rapid-sequence IVP tends to become more frequently positive.[1]

The use of VEU has both theoretic and practical advantages over rapid-sequence studies as the screening test for hypertensives. The theoretic advantages of the dynamic test include: (1) the ability to detect bilateral circulatory defects; (2) only lesions significant enough to cause almost total loss of vasodilator reserve are detected, whether large or small vessel disease is responsible; and (3) some idea of vasodilator reserve in the contralateral kidney is obtained.

Many authors have noted that surgical results can be strongly dependent on the circulatory state of the "normal" kidney. In regard to the latter, we are intrigued by the observation that patients in whom contralateral renal vasodilatation occurred during trimethaphan hypotension were surgically curable by nephrectomy, whereas no patient who failed to show vasodilatation was benefited by nephrectomy.[13] The analogy to dynamic testing of vasodilator reserve is obvious.

The practical advantages include the superior accuracy and considerable economy. Fewer expensive hospital work-ups are initiated for false positive studies. The test itself results in a halving of roentgenograms taken and a similar reduction of technician time.

The following protocol is recommended for routine use:

1. Bowel cleansing with cathartics and clear liquid diet.
2. Nothing by mouth for 8–12 hours.
3. Obtain preliminary roentgenogram, determine if the silhouettes of both kidneys are visible
   a. if not, plan to obtain a coned roentgenogram of kidneys 30 seconds after contrast medium bolus injection.
4. Inject intravenous contrast medium bolus in the usual amounts.
5. Obtain 5 and 10 minute full field roentgenograms without compression to define the anatomy of the kidneys, pelves, ureters, and bladder.†
6. After satisfactory delineation of urographic aspects of the study, inject 50 mg. ECA (or 40 mg. furosemide, Lasix) intravenously along with a dilute contrast medium infusion (approximately 5 mg./ml. iothalamate) to maintain the nephrogram.

† Others may prefer their own routine procedure for demonstrating urinary tract morphology. Flexibility is desirable and possible with one constraint. The combination of contrast agent and ethacrynic diuresis makes it increasingly difficult to maintain a satisfactory nephrogram if step 6 is delayed much beyond 10 minutes.

7. Obtain coned film of kidneys 10 minutes after vasodilator injection.
8. Estimate observed renal silhouette increase by planimetry, or length times width, on films from Steps 3 and 7.

VEU is still recommended only as a screening test and must be followed by arteriography, selective renal vein renins, and/or split function testing prior to surgery. Our experience with the normal VEU response in patients with incidental stenosis is too sparse to be definitive. Interestingly enough, Dorph and Oigaard[7] have recently confirmed both the increased accuracy of dynamic size changes over contrast disparity and the normal size increase with insignificant stenosis on a retrospective analysis of several hundred urea-washout studies. Since hypertonic urea is both a good renal vasodilator and a fair diuretic, the search for better screening tests has come full circle. Hopefully, the physiologic bases of such tests are better understood from more recent research.

SUMMARY

The use of dynamic increases in renal size as determined by the technique of vasodilated excretory urography (VEU) is compared with modified rapid-sequence pyelography in a series of 250 hypertensives.

The physiologic constraints of contrast disparities in screening for significant renal arterial stenosis are discussed.

Normal and abnormal responses to VEU are defined as well as laboratory evidence that renal size and renal hemodynamic states are closely linked. Thus, changes in renal size elicited by vasodilators can be used to assess renal vasodilator reserve and, thereby, the presence or absence of significant stenosis. Size changes are shown to be more accurate than contrast or length disparities.

None of the kidneys that increased by 10 per cent or more had significant stenosis; all of the kidneys with significant stenosis increased by 5 per cent or less.

The use of VEU has many advantages in screening hypertensives for renovascular hypertension that is potentially curable.

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