Pharmacoangiographic Manipulation of Renal Collateral Blood Flow

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SUMMARY Vasodilatory or vasoconstrictive renal pharmacoangiography was applied in investigating the significance of 50 renal artery stenoses. The technique involves comparison of selective magnification renal arteriograms before and after intra-arterial injection of epinephrine or acetylcholine, seeking changes in direction of flow in potential collateral routes. The drug injected depended upon the hemodynamic conditions during control arteriography. Final determination of significance depended on response to surgery in most patients, and renin levels in a few. Vasoconstrictive angiography was determinate in 18/26 (69%) of significant stenoses and correctly identified hemodynamic significance in each. Other angiographic signs of collateral circulation were present in seven of the other eight significant stenoses studied with the vasoconstrictive method. Vasodilatory pharmacoangiography was determinate in 20 arteries, and correctly evaluated each of nine significant and 11 insignificant lesions. Pharmacoangiography is a moderately sensitive and completely specific angiographic method for evaluating the hemodynamic significance of renal artery stenoses.

REDIRECTION OF blood flow in poststenotic nonparenchymal renal arteries by pharmacoangiographic manipulation has previously been suggested as a sensitive and specific index of clinically and hemodynamically significant renal artery stenoses. Despite promising initial results, the technique has not been widely accepted; indeed it seems to have been largely ignored. Reassessment of our earlier experience via an expanded series was undertaken to confirm or disprove the validity of this technique in establishing the importance of renal artery occlusive lesions.

Methods and Materials

Vasoconstrictive and vasodilatory renal pharmacoangiographic methodology has previously been reported. The technique augments angiographic demonstration of existing or potential collateral flow, and the logic involved in applying and interpreting results has been elaborated (fig. 1). Pharmacoangiography was generally reserved for cases where hemodynamic significance of a demonstrated stenosis was suspected but collateral circulation was not demonstrable. In patients with distinct collateral flow circumventing a stenosis, hemodynamic significance was clearly indicated and pharmacoangiography was unnecessary. Minimal irregularities reducing luminal diameter by less than 25% were considered insignificant and not investigated pharmacoangiographically in this series.

After informed consent was obtained, the angiographic examination was begun with an aortogram in order to demonstrate the number of renal arteries, gross stenoses, and opacified collateral circulation. In the absence of orificial stenoses precluding selective catheterization, bilateral magnification selective arteriography was performed using 8 ml of contrast medium injected in about 1.2 sec. Films were then carefully inspected, searching particularly for evidence of arterial stenoses, collateral circulation, presence or absence of poststenotic opacified nonparenchymal arteries, or signs of small vessel or parenchymal disease.

If the control arteriograms did not reveal nonparenchymal arteries arising distal to a stenosis, vasoconstrictive pharmacoangiography was performed. For this technique, 3 or 4 µg of epinephrine, diluted in 3 ml of saline, was rapidly injected into the renal artery, followed immediately by an arteriogram, using 7 or 8 cc of contrast media injected over about 2 sec (fig. 2). If this arteriogram still did not demonstrate opacified poststenotic nonparenchymal branches, an additional vasoconstrictive study was sometimes performed using 6 or 8 µg of epinephrine.

If the control arteriogram demonstrated opacification of small nonparenchymal arteries arising beyond the stenosis (fig. 3), vasodilator pharmacoangiography was performed. For vasodilation, 80 µg of acetylcholine per minute were infused for 5 min, followed within 10 sec by repeat arteriography with 10 cc of contrast medium injected in about 1.2 sec. Modification of dose and injection rate of contrast medium was necessary to maintain angiographic quality in the presence of marked drug-induced changes in renal blood flow.

Consecutive magnification pharmacoangiograms were reviewed from 49 patients with renal artery stenosis. Five cases were eliminated because of incomplete data, leaving 44 patients for analysis (table 1). Thirty-three of these patients had essentially unilateral, and 11 bilateral stenoses, for a total of 55 renal artery stenoses. Fifty of these renal arteries had pharmacoangiography, and five did not. These 50 pharmacoangiograms were reviewed by two of us (JJB and JFW) without knowledge of renin assay or operative result, and any differences of opinion were resolved by discussion. Review and prospective diagnoses agreed in 44 of the 50 stenoses. In the six where prospective and review diagnoses disagreed, the review interpretation was used for analysis.

Of the 44 patients, 29 were women and 15 men. Pharmacoangiography was performed in 34 arteries with fibromuscular dysplasia (31 from women and three from men) and in 15 atherosclerotic arteries (three from women and 12 from men). One graft stenosis was studied in a woman. Vasoconstrictive pharmacoangiography was performed in 29 arteries of 28 patients, and vasodilatory pharmacoangiography in 21 arteries of 20 patients (four patients had both vasoconstrictive and vasodilatory studies).
**FIGURE 1.** Application and interpretation of pharmacoangiography.

- **CONTROL ARTERIOGRAM**

- **APPROPRIATE TECHNIQUE**
  - Vasoconstrictive pharmacoangiography (3-8 μg epinephrine)

- **PHARMACOANGIOGRAM**

- **CONCLUSION**
  - Flow in PNPA reversed. Stenosis hemodynamically significant.
  - No change. Stenosis indeterminate significance. Possible congenital absence of appropriate small arteries.

- **PNPA identified**

- **Vasodilator pharmacoangiography (80 μg acetylcholine per min x 5 min)**

- **Reversal of flow in PNPA. Stenosis hemodynamically significant.**

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**FIGURE 2.** Vasoconstrictive pharmacoangiography, significant stenosis. E.T., a hypertensive woman. Renal vein renin ratio, R/L 1.64. No operation. Left) Control arteriogram demonstrates atherosclerotic stenosis of the main renal artery. There is absent distal orthograde flow in poststenotic nonparenchymal arteries. A faint dilution defect is suggested (arrow). Right) Repeat arteriogram after 3 μg of epinephrine. Distal orthograde flow is now present in poststenotic nonparenchymal arteries (arrows) proving the presence of collateral circulation on control arteriograms. The distal arrow indicates an artery arising from the site of the previously suggested dilution defect.
For this investigation, reversal of direction of flow in non-parenchymal renal artery branches arising distal to a stenosis, occurring between control and pharmacoangiograms, was considered the sole angiographic criterion of a hemodynamically significant stenosis. Failure to reverse flow in these vessels was considered the angiographic criterion of an insignificant stenosis. If poststenotic non-parenchymal branches of the renal artery were never opacified, a situation anticipated in 4% of the population, the significance of the stenosis was considered indeterminate by pharmacoangiography.

Final designation as a clinically significant stenosis was based on favorable results of appropriate operation, as defined by the Cooperative Study of Renovascular Hypertension, or in a few cases without operation, upon selective renal vein renin assays. Plasma renin activity was determined by the immunoassay method of Haber; a renal vein renin ratio of 1.4 or more, comparing the ischemic to the contralateral kidney, was designated significant. Specimens for renin assay were obtained under a variety of conditions, but sodium restriction, administration of diuretics, and sampling with the patient in the upright position were usually part of the preparation.

Final designation as a clinically insignificant stenosis was based on failure of a technically satisfactory ipsilateral operation, favorable result after contralateral operation, or in those patients not undergoing operation, on normal selective renal vein renin assay. Hypertensive urography, radioisotope renograms, and peripheral renin assays were not considered in determining final designation of significance or insignificance in this analysis.

### Results

**Vasoconstrictive Pharmacoangiography**

Among 18 stenoses considered significant by vasoconstrictive pharmacoangiography, all were proven to be clinically significant (table 1). In addition, seven of 11 stenoses classified as indeterminate by pharmacoangiography had other angiographic criteria of significance. In five cases, collateral arteries were faintly opacified on arteriography, or dilution defects were suspected on selective arteriography, but collateral infow could not be reversed by the dose of epinephrine selected. In two other instances, redirection of flow in poststenotic arteries occurred on sequential examinations performed weeks or months apart, despite the fact that reversal could not be achieved with vasoconstrictive pharmacoangiography during a single procedure. The remaining four indeterminate stenoses had no angiographic evidence whatsoever suggesting significance. Three of these proved to be insignificant by renins or operation, and one with unilateral renin evaluation has yet to undergo operation.

Thus of 26 renal artery stenoses proven to be clinically significant by criteria indicated above, significance was predicted by vasoconstrictive pharmacoangiography in 18, and by other angiographic evidences of collateral circulation in seven. There were no false positive arteriographic diagnoses of significance. Pharmacoangiography provided the only preoperative sign of significance in three stenoses, and directly demonstrated collaterals were the only preoperative sign of significance in a fourth. Renin assay was misleading in two of 22 cases in whom selective renal vein renin assay was performed.

**Vasodilatory Pharmacoangiography**

Ten renal artery stenoses were designated significant by vasodilatory pharmacoangiography. Confirmation of clinical significance was available in nine, and is pending in one. Eleven stenoses were classed as insignificant by vasodilatory pharmacoangiography (fig. 4). Confirmation of clinical insignificance was obtained in each instance. Thus in 20 determinate cases, sensitivity and specificity of the vaso-

### Table 1. Pharmacoangiography. Renal Artery Stenosis (50 Arteries)

<table>
<thead>
<tr>
<th>Category</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Epinephrine</td>
<td>29 arteries</td>
</tr>
<tr>
<td>a. Significant by pharmacoangiography</td>
<td>18</td>
</tr>
<tr>
<td>Confirmed</td>
<td>18</td>
</tr>
<tr>
<td>High renin, op result good</td>
<td>13</td>
</tr>
<tr>
<td>High renin, no operation</td>
<td>2</td>
</tr>
<tr>
<td>No renin, op result good</td>
<td>2*</td>
</tr>
<tr>
<td>Normal renin, op result good</td>
<td>1*</td>
</tr>
<tr>
<td>b. Indeterminate by pharmacoangiography, significant by ordinary angiography</td>
<td>7 arteries</td>
</tr>
<tr>
<td>i. Significant by angiographic evidence of collateral circulation, but collaterals not reversed by up to 8 μg of epinephrine</td>
<td>5</td>
</tr>
<tr>
<td>High renin, no operation</td>
<td>2</td>
</tr>
<tr>
<td>High renin, op result good</td>
<td>2</td>
</tr>
<tr>
<td>High contralateral renin, cure after ipsilateral bypass</td>
<td>1*</td>
</tr>
<tr>
<td>ii. Significant by altered flow in extrarenal arteries between different examinations, but not reversed by epinephrine (1 patient)</td>
<td>2 arteries</td>
</tr>
<tr>
<td>Significance confirmed by transient cure after unilateral bypass, then recurrence, then improvement after bypass of the remaining kidney. High renin bilaterally</td>
<td></td>
</tr>
<tr>
<td>c. Indeterminate by pharmacoangiography and ordinary angiography</td>
<td>4 arteries</td>
</tr>
<tr>
<td>Failure after postgraft nephrectomy</td>
<td></td>
</tr>
<tr>
<td>no renin</td>
<td>1</td>
</tr>
<tr>
<td>Equal renin, no operation</td>
<td>2</td>
</tr>
<tr>
<td>High renin — no operation yet (considered significant)</td>
<td>1</td>
</tr>
<tr>
<td>d. Summary</td>
<td></td>
</tr>
<tr>
<td>True positives — 69% (18/26)</td>
<td></td>
</tr>
<tr>
<td>False positives — 0%</td>
<td></td>
</tr>
<tr>
<td>2. Acetylcholine</td>
<td>21 arteries</td>
</tr>
<tr>
<td>a. Significant by pharmacoangiography</td>
<td>10</td>
</tr>
<tr>
<td>Confirmed</td>
<td>9</td>
</tr>
<tr>
<td>Renin ratios 1.4 or more, op result good</td>
<td>4</td>
</tr>
<tr>
<td>Renin ratio 1.29, op result good</td>
<td>1*</td>
</tr>
<tr>
<td>High renin, no operation</td>
<td>2</td>
</tr>
<tr>
<td>No renins, op result good</td>
<td>2*</td>
</tr>
<tr>
<td>No confirmation as yet</td>
<td>1</td>
</tr>
<tr>
<td>b. Insignificant by pharmacoangiography</td>
<td>11</td>
</tr>
<tr>
<td>Confirmed</td>
<td>11</td>
</tr>
<tr>
<td>Low renins, good results after contralateral op</td>
<td>2</td>
</tr>
<tr>
<td>Low renins, failure after ipsilateral op</td>
<td>2</td>
</tr>
<tr>
<td>Low renins only (1 was high initially), no op</td>
<td>6</td>
</tr>
<tr>
<td>High renins, failure after nephrectomy</td>
<td>1*</td>
</tr>
<tr>
<td>c. Summary</td>
<td></td>
</tr>
<tr>
<td>True positives — 100% (9/9)</td>
<td></td>
</tr>
<tr>
<td>True negatives — 100% (11/11)</td>
<td></td>
</tr>
</tbody>
</table>

*Angiography crucial in predicting significance or insignificance.
dilator technique was 100%. Vasodilatory pharmacoangiography provided the only preoperative index of clinical significance in three of these cases.

Other Observations
No patient showed significant deleterious effect from the pharmacoangiography. A mild and transient elevation of blood pressure, about 5 mm Hg systolic, generally followed epinephrine injection. No systemic effects of acetylcholine infusion were noted. In one patient, a subintimal injection occurred during selective renal catheterization, but no pharmacologic agent had been injected.
Twelve patients had azotemia, as manifest by serum creatinine of 1.4 to 2.3 mg% and/or blood urea nitrogen of 25 to 53 mg%. Nine of these patients had an angiographic diagnosis of significant stenosis; eight had a favorable result after operation, and one has not undergone operation. One patient had surgery despite an angiographic diagnosis of bilateral infarcts and insignificant stenoses, and was an operative failure. One patient with serum creatinine 2.3 mg% had an angiographic diagnosis of nephrosclerosis and insignificant stenosis; bypass was not performed. The twelfth patient had diagnosis of insignificant stenosis and operation was not performed (fig. 4).

Angiographic evidence of renal parenchymal or small vessel disease was noted in the two patients cited above, and in one other patient with a significant stenosis and contralateral renal tuberculosis. Renovascular operation was not performed in this latter case.

Discussion

Differentiation of clinically significant and insignificant stenoses of the renal artery is a diagnostic problem with immediate therapeutic implication. A considerable body of clinical and laboratory data indicates that stenoses causing hypertension are of hemodynamic significance and are associated with a transstenotic pressure gradient. The variability of the pressure gradient in renal artery stenosis was experimentally demonstrated by Thomas et al. and Lupu et al. Manipulations which increased blood flow and reduced peripheral vascular resistance, such as injection of isoproterenol or postocclusive hyperemia, increased the gradient; injection of 1-2 µg/kg of epinephrine intravenously abolished or markedly reduced the pressure gradient. Analogous pharmacologic manipulation of pressure gradient provides the basis for the current technique. As the gradient is increased, collateral flow is augmented; as the gradient is decreased, collateral flow is reduced or abolished. The resultant change in direction of flow in collateral pathways enables recognition of their collateral function.

Although angiographic signs correlate logically with hemodynamic significance (i.e., pressure gradient), the strong correlation between hemodynamically and clinically significant renal artery stenoses enables indirect prediction of clinical significance from the angiogram. Although there may be other hemodynamic sequelae of renal artery stenosis, such as decreased flow, decreased pulse pressure, and decreased pulse flow, a pressure gradient has been present consistently in experimental renal artery stenoses which caused renovascular hypertension. Furthermore, in the acute experimental situation, there is good correlation between transstenotic pressure gradient, systemic pressor response, and increase in renin production. The occasional absence of a detectable pressure gradient in clinically significant renal artery stenoses is probably attributable to increase in peripheral renovascular resistance and consequent reduction of transstenotic flow and pressure gradient that may occur secondary to anesthesia, operation, or intra-arterial passage of a recording needle.

Proper application and interpretation of this method requires full understanding of several hemodynamic concepts, and used by inexperienced trainees, the method has a large potential for error. Multiple nonparenchymal arteries normally originate from the distal main renal artery, primary rami, segmental arteries or arcuate arteries (fig. 5). These extrarenal vessels include capsular, ureteral, pelvic, and...
adrenal branches that inosculate in the retroperitoneum with arteries from other sources. In 96% of normal patients, one or more of these arteries opacify at the time of selective renal arteriography.17

In patients with functionally significant renal artery stenoses, nonparenchymal branches arising beyond the stenoses are usually not opacified on selective arteriograms. Because of the pressure gradient, these arteries derive their blood flow from nonrenal sources, carrying collateral flow toward the kidney. Thus, observing the presence or absence of orthograde flow in poststenotic nonparenchymal arteries after selective arteriography assumes discriminatory value in differentiating hemodynamically significant from inert stenoses.17

Classification of the significance of a stenosis however, solely on the basis of presence or absence of distal orthograde flow in poststenotic nonparenchymal arteries can be misleading for two reasons, and pharmacoangiography is required to avoid error.

1) Nonparenchymal arteries with orthograde flow are not detectable angiographically from approximately 4% of normal renal arteries.1 Therefore, absence of orthograde flow need not always represent reversed flow due to collateral circulation. When poststenotic orthograde flow is absent on ordinary arteriograms, significance is likely, but vasoconstrictive pharmacoangiography is required for more reliable evaluation. Vasoconstrictor markedly decreases renal blood flow and virtually eliminates the pressure gradient across the stenosis, if one exists. If distal nonparenchymal arteries are truly present, they will opacify after vasoconstrictor pharmacoangiography proving 1) their existence, and 2) that they were conducting blood in retrograde direction and functioning as collaterals. If distal orthograde flow does not occur after pharmacoangiography with epinephrine, the study must be considered indeterminate. Poststenotic nonparenchymal arteries may simply not be present, or the dose of epinephrine may be improper (infra vide). The significance of the stenotic lesion must then be assessed by other means.

2) In approximately 15% of cases harboring clinically significant stenoses, orthograde flow occurs in poststenotic nonparenchymal arteries during standard selective arteriography.2 It is postulated that in these instances peripheral renovascular resistance is high and transtenotic pressure gradients have been transiently reduced or eliminated. Thus, orthograde flow does not always imply that a stenosis is hemodynamically inert. In such cases, vasodilatory pharmacoangiography minimizes peripheral renovascular resistance, and maximizes transtenotic blood flow and pressure gradient. Under these conditions of maximal gradient, persistent orthograde flow in poststenotic nonparenchymal arteries is considered indicative of an insignificant stenosis. If orthograde flow disappears following vasodilation, the stenosis is significant.

The pharmacoangiographic technique described herein is based on the following postulates: 1) Clinically significant stenoses of the renal artery are always associated with a pressure gradient under conditions of peripheral vasodilation; 2) potential renal collateral arterial routes are abundant; 3) collateral flow will occur when the pressure gradient across the stenosis equals or exceeds the pressure gradient across the collateral pathway; 4) flow in collateral vessels always indicates a transtenotic pressure gradient; and 5) the peripheral renovascular bed has appreciable vasoactivity. The validity of the pharmacoangiographic method provides support for each of these tenets.

Independent support for the aforementioned postulates is also available. Postulate (1): experimental and clinical correlation between transtenotic pressure gradients and renovascular hypertension has already been mentioned.4-18 Postulate (2): the usual abundance of potential collateral routes has been amply documented by several clinical and experimental angiographic studies.17, 18 Postulates (3) and (4): it is axiomatic that flow through relatively long, narrow and tortuous collateral channels is associated with a pressure drop. There must be an equivalent pressure gradient across the stenosis; otherwise collateral flow would not occur. Finally, Postulate (5): the reactivity of the peripheral renovascular bed has been adequately documented. Severe peripheral vasoconstriction results from intra-arterial injection of epinephrine20-21 or angiotensin.19, 21 Vasodilator reserve of the kidney from the basal state is only modest.22 Marked vasodilation, however may occur if peripheral arteries are already constricted.

Comment

In the present study, effects of acetylcholine or epinephrine in normal arteries, or in arteries with stenoses reducing diameter by less than 25%, were not evaluated. Such studies however were recorded in a previous paper,1 where no change in direction of flow in extrarenal arteries was observed.

Deleterious effects of intrarenal acetylcholine infusions have not been reported to our knowledge. Redman et al.14 found no histologic changes in rabbit kidneys after selective intra-arterial injections of 0.5 or 2 μg/kg epinephrine; minor injury was produced by 4 μg/kg. However, if 0.5 cc of 76% diatrizoate was injected shortly after epinephrine, then epinephrine injections of only 0.5 or 1.0 μg/kg were associated with some histologic damage. In our patients, epinephrine doses were only about one-tenth this amount, and no deleterious morphologic or functional effect was observed.

Variability in the optimal dose of epinephrine may be one reason for the appreciable number of indeterminate vasoconstrictor studies in this series. An excessively small dose might not adequately reduce the pressure gradient; too large a dose may prevent flow of contrast agent to the origin of the extrarenal branches. In several stenoses, 3 or 4 μg of epinephrine did not reverse flow in poststenotic collateral vessels, whereas 6 or 8 μg did. Thus, larger doses may be necessary if smaller ones yield indeterminate results. If poststenotic nonparenchymal arteries are never visualized, then diagnosis is indeterminate. It must be emphasized that indeterminate results of vasoconstrictive pharmacoangiography are not misleading, and are not to be considered errors.

One source of failures of renovascular surgery has been operation upon hemodynamically inert stenoses. Pharmacoangiography helps eliminate this type of improper selection. In the present series, all operated patients whose stenoses appeared significant by pharmacoangiographic techniques had a favorable surgical response.
Analogous techniques may be applied in assessing stenotic lesions in other vascular beds having considerable vasoactivity. Recent work has shown redistribution of intramyocardial blood flow with experimental coronary artery stenoses when pre- and post-vasodilated arteriograms are compared. Redistribution of myocardial blood flow has also been recognized clinically on pre- and post-vasodilated perfusion scans.

Conclusion

Pharmacoangiography is a reliable method for distinguishing hemodynamically significant from inert stenoses of the renal artery. The method requires certain refinements in equipment and interpretation which may slow general acceptance. When properly applied however, it may be more accurate than renin assay. In the present series, operation on patients with pharmacoangiographic evidence of hemodynamically significant stenoses invariably produced a favorable response. The principles of pharmacoangiographic redistribution of blood flow may be applicable in assessing stenotic lesions of other reactive vascular beds.

References

Pharmacangiographic manipulation of renal collateral blood flow.
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