wise increases. The lung apexes behave like Zone I, the midzone portions like Zone II, and the bases like Zone III. 4

In various lung diseases alveolar pressures may become substantially elevated as a result of alterations of ventilatory mechanics. Regional alveolar pressures may become higher than pulmonary-artery pressure, leading to cessation of flow. Elevation of the thorax would lower pulmonary arterial pressure (by gravitational effect) in the upper lung zones, accentuating the decrease in pulmonary blood flow. 7

The application of these considerations to the phenomenon of platypnea requires the assumption that diffuse obstructive emphysema is accompanied by widespread areas of lung in which alveolar pressures are markedly elevated. This will potentially produce a diffusely scattered Zone I owing to elevated alveolar pressures. The assumption of an upright position would increase this tendency by lowering pulmonary-artery pressure in the upper parts of the lung. The combination of the two effects could produce a substantial compromise of regional blood flow. Such regions would act as respiratory dead space (ventilated but unperfused segments of the lung). This increase in dead space would be associated with hyperventilation, increasing the work cost of breathing and, in turn, producing dyspnea. Hyperventilation would augment air trapping, with further increases in alveolar pressure, initiating a vicious circle. Increases in alveolar pressures would raise flow resistance in an already compromised pulmonary vascular bed. This increase in flow resistance could decrease left ventricular filling and hence lower left ventricular output. The resumption of the supine position would then reverse this chain of events by supplying a more uniform distribution of pulmonary-artery pressures that were higher than alveolar pressures.

Although this explanation for platypnea is speculative, it does fit both the clinical and the laboratory observations. Regardless of the validity of the mechanisms hypothesized, it seems important to record this rare but fascinating manifestation of severe chronic obstructive lung disease.

REFERENCES


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A Publication of the American Physiological Society

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PHYSIOLOGIC CONSEQUENCES OF RENAL ARTERIAL STENOSIS*

HARRETT P. DUSTAN, M.D.

ONCE upon a time, not so very long ago, there were two women — both 35 years old, and both with hypertension of recent onset. One had severe, sustained diastolic hypertension and intense retinal arteriolar constriction with hemorrhages and exudates; the serum potassium was 3.0 mEq per liter. The other had mild labile hypertension, mild retinal arteriolar constriction and a serum potassium of 4.2 mEq per liter. In each, the urogram showed the right kidney to be 1.5 cm shorter than the left. Although the contrast material appeared one minute later in the right kidney, by 10 minutes it was more concentrated than on the left. Renal arteriography, in each, showed a stenosis of the right main renal artery, and during ureteral urine collections the right kidney excreted urine of lesser volume and sodium concentration than the left. In each, renin activity of blood obtained from the right renal vein was greater than that from the left. All these findings suggested that both patients had hypertension as a consequence of renal arterial stenosis, and surgical treatment seemed indicated. However, before operation each patient was treated differently. In the patient with severe diastolic hypertension, guanethidine was used to achieve substantial lowering of arterial pressure for three weeks before operation. The one with the mild labile hypertension was taught how to measure her own arterial pressure and went home for a month to obtain an adequate preoperative record. In each, operation was then performed. In one, the lesion was resected, and an end-to-end arterial anastomosis performed; in the other, a bypass, aortic-renal-artery graft was done. After operation arterial pressure became normal in both and remained so.

These patients exemplify many of the consequences of renal arterial stenosis: changes in salt and water excretion; effects on renin release; hypertension — mild or severe — and responsive to a drug that suppresses sympathetic adrenergic activity; and sec-

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The possibility that renal arterial stenosis could cause hypertension arose in the 1930's with Goldblatt's description of an experimental form of hypertension caused by arterial clamping. Soon thereafter a mechanism for the hypertension was provided by discovery of the renal pressor system by Page and Helmer and Braun-Menendez et al. However, clinical recognition of such lesions had to wait until the 1950's, when contrast materials safe enough for use in arteriography became available. Howard and his co-workers are to be credited with the first clear description of renovascular hypertension. They showed the value of renal arteriography in demonstrating stenoses, the importance of urographic signs in suggesting their presence and the abnormalities in renal excretory function that may result.

Now, some 15 years later, technics for diagnosis of renal arterial occlusive disease are firmly established. Unfortunately, there are as yet no ways of determining with complete certainty that a lesion is causing hypertension without the therapeutic test of a technically successful surgical procedure.

With the exception of arteriography, all the diagnostic tests reflect the physiologic effects of stenosis. A review of these should help not only in interpretation of results obtained but also in an understanding of their limitations. But first a discussion of the stenoses themselves seems necessary.

**Renal Arterial Occlusive Diseases**

There are a number of arterial diseases that produce stenosis. The most frequent is atherosclerosis. This is found most often in men and usually after the age of 45. In contrast, the nonatherosclerotic lesions occur primarily in young or middle-aged women, children, teen-agers or young men. Considerable confusion surrounds the nomenclature of these lesions, reflecting, in large measure, a lack of agreement between "the lumpers and the splitters." The former categorize all of them under a general heading of fibromuscular hyperplasia, or fibromuscular dysplasia, and the latter recognize four types, depending on the primary location of the lesion in the vessel wall and its predominant tissue composition. These four types are intimal fibroplasia, medial fibroplasia, fibromuscular hyperplasia and subadventitial fibroplasia. To us this classification has advantages because distinctive features permit histologic diagnosis from arteriograms and because each lesion seems to have its own natural history.

**Physiologic Effects of Stenosis**

**Changes in Pressure and Flow**

Regardless of the nature of the stenosis, it has the capability of producing a pressure gradient. The fact that a gradient has not always been found at operation in such patients may be related to intrarenal vascular resistance. This is an important consideration because the necessity of a pressure gradient to renovascular hypertension is a widely held opinion, and failure to find it is sometimes looked upon as a contraindication for surgical treatment. That intrarenal vascular resistance plays a part in determining arterial pressure distal to a stenosis is indicated by the experiment of Thomas, Brockman and Foster. They showed in dogs that the gradient produced by a Goldblatt clamp could be abolished or much diminished by intrarenal vasoconstriction after hemorrhage or administration of pressor amines and exaggerated by renal vasodilatation after administration of isoproterenol directly into the renal artery. Thus, it seems that failure to find a gradient should not be accepted as an absence of one until the measurement has been repeated during renal vasodilatation, produced by isoproterenol or some other vasodilating drug.

Total renal blood flow is often reduced by renal arterial stenosis. How essential this is to the physiologic consequences of stenosis is not certain; at least renin release can be evoked experimentally by a reduction in perfusion pressure without a reduction in flow. Intrarenal vascular resistance must be as important in determining volume of flow through a narrowed artery as it is in the absence of stenosis. Furthermore, variations in distribution of intrarenal flow may well have a major role in the physiologic consequences of stenosis. For instance, a slowed medullary flow could increase tubular reabsorption of sodium and water, and a preferential decrease in cortical flow could decrease glomerular filtration rate. In the latter regard, Hollenberg et al. using the xenon washout technic, have shown a disproportionate decrease in cortical blood flow in patients with renal arterial stenosis.

**Effects on Renal Excretory Functions**

Renal arterial stenosis modifies excretory functions in characteristic ways, depending on whether the lesion is unilateral or bilateral or whether the whole kidney or only a segment is affected. Reasons for the changes are not apparent; possible explanations are reduced perfusion pressure, decreased total flow or a modification of its intrarenal distribution. Whatever the mechanism, the result is usually a difference in function of the two kidneys that is reflected in the urographic signs of renal arterial disease, results of split function tests and renographic differences.

It is helpful to consider the studies done in dogs because they explain much of what is found in the evaluation of patients with renovascular hypertension.

**Experimental studies.** In 1954 Howard and his colleagues reported that in some of their patients
with "impaired blood flow to the kidney" urine from the affected side was of smaller volume and lower sodium concentration than that from the unaffected side. This was the clinical counterpart of experiments done in dogs a few years before by Mueller et al.,12 in which partial ligation of one renal artery, sufficient to reduce glomerular filtration rate moderately, produced a marked decrease in water and sodium excretion. However, when the "untouched" kidney was removed, the remaining one, still perfused through a narrowed artery, promptly increased salt and water excretion to the amount previously excreted by the two kidneys; filtration rate also rose, but not so much. These studies showed not only the effects of renal arterial stenosis on excratory functions but also the importance of the "unaffected" kidney in permitting their expression.

Berliner, Davidson and Levinsky13-15 have provided the most thorough experimental analysis of the effects of unilateral main renal arterial narrowing. These experiments contributed much to the current concepts concerning the central roles of sodium and urea reabsorption in urinary diluting and concentrating mechanisms.

In the proximal tubule, active sodium reabsorption provides the driving force for reabsorption of chloride and water. The concentration of urea is accordingly raised, resulting in a concentration gradient that allows outward transfer of a considerable fraction of the filtered urea. In the ascending limb of the loop of Henle reabsorption of salt, but not of water, takes place, and this begins the process of urinary dilution. In addition, it provides solute to raise the osmolality of the medullary interstitial tissue and set the stage for urinary concentration. As filtrate passes into distal tubules and then into collecting ducts, sodium reabsorption continues the process of urine dilution. When the amount of sodium available for reabsorption is limited, especially in distal portions of the nephron, the consequences of this limitation are expressed as qualitative changes in excratory function.

Narrowing of the renal artery either artificially or by an occlusive lesion produces these qualitative changes because, with the reduction in filtration rate that accompanies stenosis, filtered sodium load is decreased. The proximal tubule reabsorbs its quantity, which represents a proportionately greater fraction of the filtered load than it normally reabsorbs. This leaves less sodium available for diluting functions in distal tubules and collecting ducts; accordingly, urine from the affected side cannot become so dilute as that from the opposite kidney.

Urea also plays an important part in determining the composition of urine under these circumstances. As glomerular filtration rate is reduced and increased fractions of salt and water are reabsorbed in proximal tubules, urea concentration of the filtrate is disproportionately increased, as are its concentration gradient and the amount that diffuses out. As filtrate passes through Henle's loop, it picks up from the medullary interstitium urea that diffused into it from collecting ducts. The amount of urea available for this cycling from collecting ducts to medulla to filtrate helps determine the osmolality of the medullary interstitium and, thus, the final concentration of the urine. This is the rationale for use of urea infusion to test function of the individual kidneys in patients with renovascular hypertension.

In summary, a kidney supplied by a narrowed artery excretes a urine qualitatively as well as quantitatively different from that of its mate. It is of smaller volume, lower sodium concentration and greater osmolality. Concentration of creatinine is raised, and if a nonreabsorbable substance like inulin or para-aminohippurate (PAH) has been administered, its concentration is also increased. These results reflect an increased fractional reabsorption of sodium and water in proximal tubules, a deficient diluting function because of inadequate amounts of sodium delivered to distal nephron segments and a potent stimulus for urine concentration provided by the recycling of urea from collecting ducts to medullary interstitium.

The above discussion relates to functional changes that occur with main renal arterial narrowing — when the entire kidney is affected. In contrast, the consequences of occlusion or stenosis of primary arterial branches in the experimental situation have not been adequately studied.13 Occlusion of a primary branch has been reported to increase filtration rate and osmolar clearance slightly in the rest of the kidney — findings indicating an absolute decrease in numbers of functioning nephrons since this results in only a quantitative change in renal excretory function.16

Thus, it seems likely that functional expressions of branch arterial lesions depend on whether the artery is completely occluded or merely stenosed, and the amount of kidney tissue supplied by that branch. For example, with complete occlusion, affected nephrons would be functionless, producing a quantitative decrease in function on that side. Conversely, stenosis of a branch supplying a large segment of kidney should produce a functional change in the affected nephrons so that urine from that side would be qualitatively, as well as quantitatively, different from that of the opposite kidney.

Clinical studies. Results of these laboratory investigations explain the clinical tests for renovascular hypertension that depend in large measure on alterations in excretory functions just described. These tests are intravenous urography, separated function tests and radiorenography. Reviews of the clinical-physiologic correlations of such tests have recently appeared.11,17-19

Intravenous urography.11,17 The most frequent urographic signs of renal arterial stenosis include disparity in length of the two kidneys, delayed ap-
pearance time of contrast material after rapid injection, disparity in concentration of the contrast medium in the two kidneys and a delayed "washout" of the radiopaque material in the affected or more affected kidney during diuresis. Urography is an important screening test for renovascular hypertension because it is easy to perform, usually presents only minor discomfort for patients and is a standard, widely accepted procedure.

Renal size is determined not only by the amount of kidney tissue but also by the intrarenal fluid volume (blood and intratubular and interstitial fluids). (The importance of this is well recognized by the surgeon who at operation sees a kidney become larger when an arterial obstruction is released, thereby increasing blood flow and glomerular filtration.) About 60 per cent of patients have been reported to have a disparity in renal length of 1.0 cm greater, and this experience indicates the importance of such measurements in hypertensive patients.

It seems likely that consideration of the normal disparity in renal length will increase the importance of such measurements in patients with renal arterial disease. Normally, the left kidney is longer than the right by 0.5 cm in men and 0.4 cm in women. Thus, a left renal arterial lesion could be reflected by a renal length of only 0.5 cm shorter than the right, whereas a right-sided stenosis should be suspected only if the right kidney measures 1.0 to 1.5 cm less than the left. Unfortunately, this possibility has not been investigated.

Urographic signs that relate to pelviccalceal concentration of contrast material depend on the amount filtered, the degree to which it is concentrated by increased fractional water reabsorption and the failure of the affected kidney to excrete a dilute urine. These signs appear when urography is performed during dehydration.

Measurement of calceal appearance time of contrast medium in each kidney is provided by rapid-sequence filming. A kidney supplied by a stenotic artery often has a sufficient reduction in filtration to delay calceal opacification. The usefulness of this recent modification of the urogram is as yet undetermined. In a recent review, this test was reported as positive in 59 of 81 patients with unilateral main renal arterial lesions. However, no assessment was given of the frequency with which this sign was the only indication of stenosis.

Pelviccalceal concentration of contrast material as judged on the urographic films taken at five, 10 or 15 minutes may be different in the two kidneys. The affected, or more affected, side may show greater or lesser opacification than the other side. If sufficient contrast material is filtered, increased fractional water reabsorption will render the shadow more dense. However, when filtration rate is much decreased, the amount filtered will not be enough to produce increased opacification even with a substantial increase in water reabsorption. Apparently, this is one of the less sensitive signs of occlusive disease because it was found in only 44 per cent of 427 patients. Intravenous administration of an osmotic diuretic — either urea or mannitol — increases the excretion of water, and when it is performed during urography, the contrast material is diluted sufficiently that the opacity lessens markedly or disappears. However, a kidney supplied by a narrowed artery cannot dilute urine, and the osmotic diuretic fails to "wash out" the contrast medium, so that the opacity persists. Although 32 of 50 patients studied by three groups had positive tests, there has been as yet no information concerning the overall value of this procedure in screening patients for renovascular hypertension.

Function tests of individual kidneys. These procedures have been used extensively because they usually reflect the presence of stenosis and are generally regarded as useful in indicating that a lesion is responsible for hypertension. In contrast to this opinion, two analyses of the available information show that such an opinion is erroneous.

Howard and Connor were the first to suggest a causal relation between renal functional changes and elevated arterial pressure in patients with stenosis. From experience gained with continued use of split function tests, they have provided criteria for establishing whether a kidney is responsible for hypertension.

These criteria include a measurement of urine volume, and, since quantitative collections of ureteral urine are often difficult, Rapoport developed a modification to circumvent this difficulty. He used urinary creatinine and sodium concentrations for calculating tubular rejection of sodium by each kidney, finding, of course, that this was less on the affected than the unaffected side because of increased fractional sodium reabsorption.

Another modification uses urea infusion to augment differences in urine flow from the two kidneys. This is based on the demonstration of the importance of urea in promoting water reabsorption. Stamey et al. have suggested criteria, based on differences in urine volume and PAH or inulin concentrations, to indicate a mainstem or branch arterial lesion responsible for hypertension.

One of the difficulties in interpreting separated tests of renal function results from the anatomic diversity in distribution of these arterial lesions. Thus, stenosis may occur in one or both main renal arteries or in a branch on one side and a main renal artery on the other or in a large or small branch supplying one or both kidneys, and, in the last example, may either completely occlude or merely narrow the vessel. With such diversity it is hard to see how tests of excretory function can have precise meaning. Added to this complexity is the fact that only in patients with unilateral main renal arterial
stenosis can one expect, with any regularity, that
the functional criteria for an "ischemic kidney" will
be fulfilled. Bilateral main arterial lesions have
varying effects on the function of the two kidneys,
and even if the test is positive, there can be no cer-
tainty that the lesser affected kidney is not partici-
pating in the hypertension. Finally, branch arterial
lesions may mimic effects of main renal arterial dis-
ease or produce segmental atrophy so severe that
the affected nephrons do not function and only a
quantitative change in renal function results. This is
the pattern most commonly associated with pyelone-
phritis, with or without hypertension.
Thus, it is not surprising that two recent
reviews11,18 show that function tests of individual
kidneys failed to indicate patients who would re-
spond to surgical treatment. Of 86 patients
benefited by operation, function tests were positive
in 83 per cent with unilateral stenosis, 50 per cent
with bilateral stenosis and 10 per cent with branch
arterial lesions.19 This combined experience clearly
shows that results of separated function tests in a
patient with occlusive renal arterial disease reflect
the site of the lesion and not the pressor mecha-
nism that it evokes.
Radioisotope renography. This procedure with
sodium iodohippurate123I, which has been used ex-
tensively in screening of patients for renovascular
hypertension, is simple and safe and should be
ideal for this purpose because renal transport of ra-
dioactive hippurate ought to be affected by arterial
stenosis as characteristically as transport of para-
aminoohippurate (PAH). The fact that this is often
so was shown in a recent review of the value of renog-
raphy in 377 patients with renal arterial disease.19
In 85 per cent the renogram indicated presence of a
lesion. Although this is a high percentage, the test
also indicated a lesion in 19 per cent of 423 pa-
tients who had none. This experience shows that
although renography is helpful in screening patients
for renovascular hypertension, it does not have the
necessary precision to allow it to be used alone.
Effects on plasma renin activity. Renin release
can be affected by a number of factors such as renal
perfusion pressure,2 hypervolemia,24 sympathetic vaso-
motor activity,25 body posture,26 plasma sodium
concentration27 and body sodium balance.28,29 This
variety of influences shows the potential complexity
of relating the renal pressor system to hypertension
accompanying renal arterial disease.
In addition, there is a large body of evidence that
angiotensin affects the autonomic nervous system
both centrally and peripherally,30 producing a neu-
rogenic component to the hypertension. In this
regard, it is conceivable that once renovascular hyper-
tension has become established, it can be main-
tained by so minimal an increase in renal pressor
participation as to be undetectable when plasma
renin activity is the only component of the system
measured.
In spite of these complexities, evidence is accu-
mulating that in most patients with renovascular
hypertension renin activity is elevated in peripheral
venous or renal venous blood (or both).31-35 The cur-
rent success of such measurements in indicating
most patients who will respond to surgical treat-
ment suggests that split function tests will eventu-
ally cease to be regarded as having prognostic value
and will be replaced by tests for participation of the
renal pressor system.
In the published reports, a small proportion of the
patients with remediable renovascular hypertension
have given no evidence of increased activity of the
renal pressor system. Because of this, various pro-
cedures have been suggested to stimulate renin re-
lease preferentially in such patients. These pro-
cedures provide stimuli known to release renin, and
operate on the principle that an affected kidney will
respond in an exaggerated fashion — presumably
because it has stores of renin that can be readily
released. They include upright posture,26,30 prepara-
tion with a low-sodium diet27 and arterial pressure
reduction with intravenously administered sodium
nitroprusside.30 At present we have no assessment
of their overall value for indicating patients with
hypertension resulting from renal arterial stenosis.

**INDIRECT PHYSIOLOGIC EFFECTS**

**Associated Hemodynamic Changes**

**Hypertension** often accompanies renal arterial
disease. That this association is not inevitable was
first shown by Eyler et al.,39 who described normo-
tensive patients with stenoses indistinguishable
from those that, in others, elevated arterial pressure.
A systematic study of these normotensive patients
has not appeared, so that there is no information
available about how they differ from their hyperten-
sive counterparts except for having normal arterial
pressure.

One outstanding feature of the hypertension ac-
companying renal arterial disease is its variability.40
Within any sizable group of patients one encounters
variations all the way from occasional elevations of
diastolic pressure to sustained diastolic hyperten-
sion of severe degree associated with malignant
hypertensive retinopathy. There are no real explana-
tions for this variability. One possibility relates to
activation of the renin-angiotensin-aldosterone sys-
tem because plasma renin activity has been shown
to be elevated in patients with exudative and hem-
orrhagic retinopathy41 who also have signs of sec-
ondary aldosteronism.29

**Cardiac output and estimates of sympathetic
function.** Hypertension is not the only hemody-
namic abnormality consequent to renal arterial
stenosis. Frohlich et al.42 have found cardiac output to be
consistently elevated in the patients they studied. These patients also had exaggerated increases in arterial pressure during head-up tilt and after the Valsalva maneuver as well as exaggerated depressor responses to intravenously administered trimethaphan (a short-acting ganglion blocker), suggesting a neural component in this type of hypertension. These findings seem the clinical expression of the neurogenic influences found in experimental renal hypertension. Furthermore, they explain why drugs that suppress sympathetic adrenergic function are often so effective in treating renovascular hypertension.45

Hormonal, Fluid-Volume and Electrolyte Changes

The importance of the renin-angiotensin system in regulating aldosterone secretion is now well established,44 and increased renin production probably explains the secondary aldosteronism that may accompany renal arterial stenosis. Slaton and Biglieri45 compared a group of such patients with a group having primary aldosteronism. The groups were similar in degree of hypokalemia and increased aldosterone excretion rates. They differed in that the patients with renovascular hypertension were hypotensive and tended to have reduced plasma volumes whereas those with primary aldosteronism had hypervolemia and increased plasma volume. Increased aldosterone production does not seem important in the plasma-volume reduction in such patients because Tarazi et al.46 have shown oligemia to be a common feature in renovascular hypertension of all degrees of severity.

DISCUSSION

During the last 15 years, renal arterial stenosis has been accepted as an important cause of hypertension. Now also, the renal pressor system is clearly understood to have an essential role in a number of inter-related physiologic systems, including adrenal-steroid production, excretion of salt and water and autonomic nervous activity. Why hypertension is often a consequence of a stenosing lesion is not known, but activation of the renal pressor system seems to be, in some way, an important part of the mechanism.

Currently, plasma renin is the only component of the system usually studied, and most methods used provide but an estimate of activity48 and not a measurement of enzyme concentration. A clear understanding of this system will become possible only when all its components can be measured simultaneously. It is to be hoped that a method such as the radioimmunoassay of angiotensin will permit the easy determination of renin, renin substrate, angiotensin I and II, the converting enzyme and the phospholipid renin inhibitor.49 In addition, it is likely that there are other components of the system, such as an activator, that are yet to be described.

REFERENCES

29. Laragh JH, Sealey JE, Sommers SC: Patterns of adrenal secretion and urinary excretion of aldosterone and plasma renin activity in

Hugh Tatlock, M.D.