FIBROMUSCULAR HYPERPLASIA OF THE RENAL ARTERIES CAUSING HYPERTENSION*

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Stenosis of the renal arteries associated with arterial hypertension is a well-recognized entity. Many years ago Goldblatt and co-workers[1] demonstrated that a partial block of a renal artery producing renal ischaemia, induced systemic hypertension. Houssay and Braun-Menendez[2] showed that an enzymatic substance, renin, was produced in the ischaemic kidney, and that this acted on serum hypertensinogen to form angiotensin, which is a pressor substance.

In addition, it has been demonstrated that the renin-angiotensin system can stimulate the secretion of

*Paper read at the 44th South African Medical Congress, Johannesburg, July 1963.

aldosterone. Webb and Hardy[3] found increased urinary aldosterone in a patient with fibromuscular hyperplasia of the renal artery. It is therefore conceivable that the renin mechanism can cause hypertension, not only by vasoconstriction, but also by the stimulation of aldosterone.

Clinically there are several well-recognized lesions causing renal artery obstruction. Others occur more rarely.

The following causes of obstruction of the renal artery have been described:

1. Atheromatous plaques of renal arteries or aorta.[4]
2. Embolism and thrombosis of renal artery.
3. Aneurysm.[5]
4. Congenital stenosis and hypoplasia.[4]
5. Aberrant renal arteries.[4, 6]
6. Pressure by muscular bands.[7]
7. Coarctation of the aorta.[8, 9]
8. Ligation of accessory renal arteries.
9. Arteriovenous fistula.[10]
10. Extrinsic pressure by retroperitoneal tumours, or an abdominal aneurysm.[11]
11. Thromboangiitis of the renal artery.[12]
12. Syphilitic arteritis.[13]
13. Trauma.[14]
14. Idiopathic aortitis of childhood and adolescence.[15]
15. Fibromuscular hyperplasia of the renal arteries.

Fibromuscular hyperplasia of the renal arteries is an uncommon lesion, but is probably next in importance to atheroma as a cause of renal artery obstruction in females. This apparently unique lesion consists of irregular zones of thickening of the media or intima causing narrowing of the artery. Between the narrow areas there may be dilatation giving the artery a beadlike or 'string of sausages' appearance.[16] It presents a typical radiological picture, which is diagnostic.

In 1938 Leadbetter and Burkland[17] described a case of a 5-year-old boy with hypertension. They demonstrated an anomaly of the right renal artery, and after nephrectomy the hypertension was relieved. A photomicrograph of the excised artery showed changes which could now be termed fibromuscular hyperplasia. Since then, isolated reports[4, 18-20] of similar cases have appeared in the American literature, and during 1962 the Mayo Clinic[21] published their experience with 23 cases, and Wylie *et al.*[22] in the same year described 35 cases. To date these have been the only two series with any significant number of patients.

CLINICAL CONSIDERATIONS

Four cases were studied in Pretoria. All were females and were aged 36, 35, 35 and 42 years. These age and sex figures can be compared with those compiled by others:

	Age	*Sex*
Mayo Clinic[21]	16 - 58 Average 34	17 females 6 males
Wylie *et al.*[22]	63% between 30 and 50 years	30 females 5 males

SYMPTOMS AND SIGNS

Three patients had symptoms which could be ascribed to hypertension, while in one the condition was discovered during a routine examination before donating blood. Only 1 patient, who had undergone a nephropexy three years previously, had a history suggesting a renal lesion. In 2 patients the hypertension was of a short duration; in the one less than 2 years, and in the other only a few months, but in 1 patient the hypertension had been present for at least 10 years, and the other for 12 years. The average pressures were 205/110, 190/110, 200/120, and 210/120 mm.Hg. The only really significant clinical sign in all 4 patients was the presence of a systolic bruit, clearly audible in the epigastric region. This sign has been stressed by Wylie *et al.*[22] who found it in 83% of their cases. In the Mayo Clinic series[21] it was found in 18 out of 20 patients. They described the bruit as of an unusually high frequency, and almost continuous with accentuation during systole.

No patients had signs of coarctation of the aorta, primary hyperaldosteronism or of primary renal disease.

SPECIAL INVESTIGATIONS

1. *Intravenous Pyelogram*

Excretory pyelograms were done in all patients. In the majority of cases these may be completely normal. The possible pyelographic changes described in patients with renal artery stenosis include:

(*a*) A difference in the size of the kidneys.

(*b*) A difference in the time of appearance and in the concentration of the contrast medium. If there is a difference in the concentration of the dye, the darker shadow is more often to be found on the side of the affected kidney.

In 1 of our patients there was a difference in the concentration of the dye on the 2 sides as demonstrated in Fig. 1, and

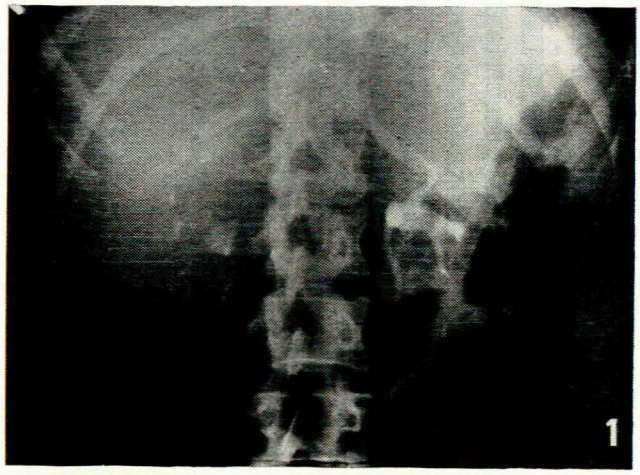

Fig. 1. Intravenous pyelogram showing a difference in the concentration of dye.

in 2 the one kidney was smaller than the other. It is of interest that in 3 patients there was severe nephroptosis of 1 or both kidneys.

2. *Separate Renal Function Studies*[23, 24]

Although the gross renal function is preserved in most cases, the affected kidney rejects abnormal loads of sodium and water, so that subnormal amounts appear in the urine. Sodium and water (i.e. volume of urine) can be measured quantitatively by separate catheterization of the ureters. This test is tedious for the patient, and subject to technical errors. However, if the plasma and urine concentrations of sodium are compared with a substance not rejected by the tubules, a significant relative reduction in sodium concentration is found on the side of the ischaemic kidney. Substances used for this purpose include creatinine, inuline and urea.[25, 26]

Separate renal-function studies were performed in 3 patients, and in all 3 some difference in function between the 2 kidneys was demonstrated. We have had no experience with the radioactive renogram.[27]

3. *Arteriography*

This is the most important investigation in cases of renal artery narrowing. Aortograms were performed by the Seldinger technique of retrograde catheterization, and by translumbar needle injection. The former method gives more satisfactory pictures. The aortograms showed the typical lesions of this disease. These consist of multiple areas of concentric narrowing of the artery, alternating with areas of normal or dilated vessel. This produces the characteristic beaded appearance[28] (Fig. 2). The proximal few millimetres of the artery are usually not affected. Fig. 3 shows involvement of the main stem, and the extrarenal branches. The beading may be localized to a small segment in some cases. In 2 of our cases the condition was bilateral. In 1 case the right renal artery was stenotic over a long distance, but the proximal few millimetres

appeared to be normal. The left kidney in this case was supplied by 3 renal arteries. Marked post-stenotic dilatation was present in 1 case.

Arteriography contributed to the definitive diagnosis of the condition, but is also essential for determining operability and method of surgical attack.

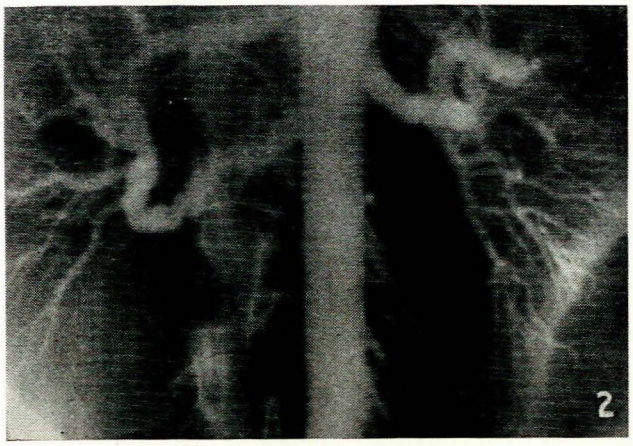

Fig. 2. The characteristic beaded appearance of the renal artery on the right side.

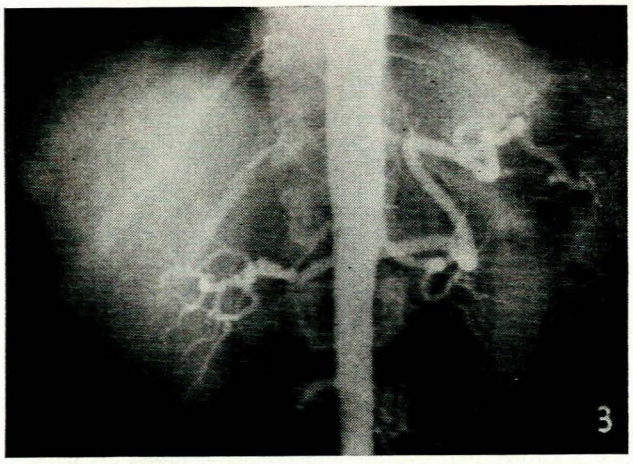

Fig. 3. The proximal few millimetres of the right renal artery are normal but the main stem and large branches are involved.

TREATMENT

In all 4 cases a diagnosis of hypertension owing to renal artery stenosis was made, and surgical exploration was advised. In 1 patient a thoraco-abdominal approach was used, but in the other 3 an antero-lateral abdominal incision proved adequate. The renal arteries were exposed from their origin to the point of entry into the kidney. In 3 patients an obvious thrill was palpable over the arteries. In 1 patient the renal artery was surrounded by numerous small vessels, which were probably collaterals. This was the patient who had had proven hypertension for 10 years. The exposed arteries presented the typical beaded appearance of the radiographs and confirmed the diagnosis of fibromuscular hyperplasia (Fig. 4). At this stage arterial pressures were determined in the aorta and in the distal portions of the renal arteries. In all 4 cases there was a marked pressure gradient across the stenotic area, confirming the diagnosis of renal artery stenosis.

Surgical procedures adopted were as follows:

Case 1

Resection of the renal artery with reconstruction by an autogenous vein graft. The saphenous vein was used for this purpose. In this case an end-to-end anastomosis without the use of a graft as advocated by Wylie *et al.*,[22] would probably have been a possible and a better procedure. At the completion of the anastomosis the pressure gradient was very small, i.e.

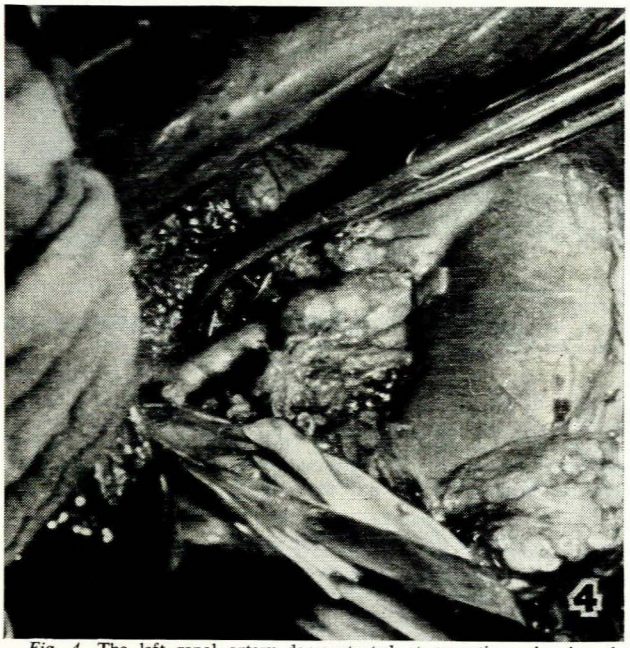

Fig. 4. The left renal artery demonstrated at operation, showing the beaded appearance.

135/110 mm.Hg in the aorta, to 115/90 mm.Hg in the distal renal artery.

This patient made an uneventful recovery. The blood pressure dropped to 120/80 mm.Hg on the 4th postoperative day.

Case 2

In this patient an attempt was made to alleviate the stenosis by a patch graft, but this was unsuccessful owing to the fact that the renal artery was too fibrotic. Resection and end-to-end anastomosis or interposition of a graft or prosthesis was not considered, as the proximal stump of normal renal artery was thought to be too short to ensure a satisfactory anastomosis. This patient had marked post-stenotic dilatation, and therefore a bypass from the aorta to the dilated renal artery was inserted, using a teflon prosthesis. Pulsation in a small upper branch of the renal artery was unsatisfactory on completion of the anastomosis, and it was decided to remove the upper pole of the kidney supplied by this branch.

Pressure readings at the completion of the operation showed only a small gradient between aorta and renal artery. The blood pressure in this patient dropped to 110/70 mm.Hg 3 days after the operation. Nine months later it fluctuated between 140/85 and 115/80 mm.Hg. In this patient a spleno-renal arterial bypass would possibly have been a better operation, as this would have eliminated the use of an artificial prosthesis.

Case 3

This patient had a small right kidney with severe stenosis of the renal artery. There was a marked difference in pressure between the proximal and distal portions of the renal artery (Fig. 5). We were in some doubt as to which would be the correct procedure to adopt in this patient, but it was eventually decided that an attempt should be made to save the kidney, and consequently a bypass between the aorta and the distal renal artery was done, using a teflon prosthesis. This resulted in a far smaller pressure gradient, i.e. 160/110 to 135/95

mm.Hg (Fig. 6). On the 4th postoperative day her blood pressure was 140/90 mm.Hg, but 3 weeks later it had risen to 175/90 mm.Hg. Three months postoperatively it was 125/85 mm.Hg.

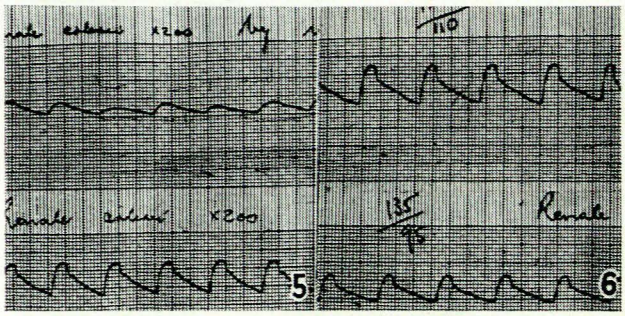

Fig. 5. Pressures taken in distal and proximal parts of renal artery and showing a marked difference in pressure.

Fig. 6. Pressures taken after insertion of a bypass prosthesis showing only a small gradient between proximal and distal parts of renal artery.

Biopsy of the kidney of this patient showed marked fibromuscular disease of the intrarenal vessels. The attempt to improve the vascularization of this kidney was therefore probably a mistake. A nephrectomy would have been a better operation. Eventually this will probably be necessary.

Case 4

This patient had bilateral disease, but separate renal function studies and radiographs showed a small left kidney with poor excretion of water and sodium. An attempt at splenorenal anastomosis was unsuccessful and the kidney was removed. Blood pressure fell from 210/120 to 160/110 mm.Hg, but the ultimate prognosis must be considered as poor.

Pathology

Three renal arteries, cases 1, 2 and 4, were available for study, and in 3 cases biopsy specimens of the kidneys were taken. The striking pathological feature is the concentric zones of mural thickening of the renal arteries causing narrowing. Immediately distal to the ring of narrowing the vessel was dilated and thin, forming a micro-aneurysm. These alternating zones of narrowing and widening gives the typical beaded appearance of the renal artery. The thickening of the arterial wall is due to fibrosis, with or without muscular hyperplasia of the media (Fig. 7). In other cases the media may appear relatively normal, and fibrosis is more marked in the intima. In 1 case from the Mayo Clinic series,[21] there was marked adventitial thickening, but this appears to be rather unusual. Fibrosis may be completely concentric or may be patchy, forming raised cushions of fibrous tissue. Fig. 8 depicts a longitudinal section of the artery showing ridges of hyperplastic tissue, alternating with troughs of mural thinning. In addition to the fibromuscular hyperplasia there is usually extensive damage to the elastic tissue. There may be fragmentation, degeneration, irregularity and duplication of the internal and external elastic laminae. These changes are most obvious in the main renal arteries, but may be found in the smaller branches, and the interlobar, arcuate and interlobular arteries.

Sections of the kidneys may show zones of cortical infarction and tubular atrophy ascribed to ischaemia. In other cases the kidney may be histologically normal.

Atherosclerosis of the main renal artery in a few cases, has been found by Wylie and his co-workers,[22] but our cases showed no such changes. There was also no evidence of arteritis or fibrinoid necrosis.

Discussion

The question arises whether these lesions are unique to the renal arteries. Poutasse and associates[18] described the case of a boy of 14 who had fibrous proliferation of the intima of the renal arteries, but also of the coeliac axis and superior mesenteric arteries. Szilagyi[29] suggested that this condition could be a local manifestation of some systemic pathologic process, such as a collagen disease.

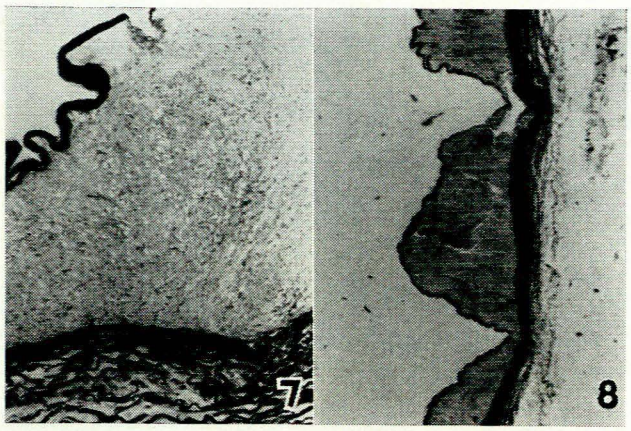

Fig. 7. Photomicrograph of renal artery showing marked thickening and fibromuscular hyperplasia of the media.

Fig. 8. Longitudinal section of a renal artery with alternating areas of thickening and thinning of the vessel wall.

Apart from these authors little other definite evidence could be found of generalized arterial disease, and, for the most part, fibromuscular hyperplasia seems to be localized to the renal arteries, although intimal fibrous stenosis may be found in other visceral arteries.

There is general agreement that these fibrous and fibromuscular stenotic lesions do not resemble atherosclerosis, although the latter may be a superimposed process. Possible aetiologic factors which have been suggested include congenital abnormalities, intrinsic defects of elastic tissue, collagen disease, Erdheim's medial necrosis, healed arteritis, and abnormal stretching of the arteries, especially in pregnancy.[19] The fact that most cases occur in young adult females may suggest the possibility of an endocrine factor, as it is known that ovarian and other hormones are capable of having an influence on mesenchymal tissues.

Hunt and associates[21] suggest a basic abnormality of elastic tissue, which may precede the fibromuscular changes, and that the latter could be an unusual healing process following some type of vascular injury.

Three of our cases displayed marked nephroptosis with rather long, tortuous renal arteries, and one is tempted to speculate whether a mechanical factor could play a role in the aetiology. As previously mentioned, 1 of our patients had a nephropexy performed some years earlier. McKusick[30] has called attention to the role of mechanical stress in the localization of vascular defects in Marfan's syndrome. His description of the pathological features of the diseased aorta in this condition is interesting: '(1) Disruption of elastic lamellae, and (2) formation of conglomerate, disorganized masses of hyperplastic and hypertrophied smooth muscle fibres.'

The possibility is suggested that the abnormal movements of a nephroptotic kidney with a long tortuous renal artery could cause so much mechanical stress that would be injurious to the elastic tissue in the arterial wall, that it could result in fibromuscular hyperplasia as a compensating process.

SUMMARY

Fibromuscular hyperplasia of the renal arteries is an important cause of renal artery stenosis and renal hypertension. It occurs predominantly in young adult females, and presents no typical clinical picture, except for the finding of an abdominal bruit, which could be helpful in the diagnosis. *The most important special investigation is the renal arteriogram* which shows a typical 'string of beads' appearance. The most striking pathological feature is the corrugated appearance of the intimal surface of the renal artery, owing to fibromuscular thickening alternating with zones of thinning. The condition is *amenable to surgical correction,* depending on the type of lesion found at operation.

I wish to thank my medical, radiological and urological colleagues for their help in the investigation of these patients, and Mr. T. Marais of the photographic department for the photographs.

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