Renin and Hypertension: A Review Article

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Physiology:

Systemic arterial hypertension can develop only as a result of an increase in the quantity of blood pumped by the heart (the cardiac output) or an increase in the resistance to flow through the blood vessels, (particularly the arterioles). These two factors are not independent: an increase in the resistance to blood flow is often the result of an excessive cardiac output which by carrying vasodilator substances away from the tissues, leads to a compensatory constriction of the arterioles (autoregulation) which eventually becomes permanent and persists after the cardiac output has returned to normal.

The renin-aldosterone system controls arterial pressure and is activated whenever there is a tendency for the pressure to fall, e.g. on standing upright, or after haemorrhage. The system attempts to restore pressure by constricting arterioles (to increase resistance to blood flow), by

producing thirst, and also by preventing the excretion of salt and water by the kidney, so that the extra-cellular fluid and blood volumes are increased and the cardiac output becomes greater. Conversely, when the arterial pressure shows a tendency to rise, the renin-aldosterone system becomes less active, i.e. it is suppressed; the arterioles relax and fluid is excreted by the kidneys so that the extra-cellular fluid volume falls and the cardiac output is correspondingly reduced. A fall in arterial pressure activates the renin-aldosterone system through receptors in the juxta-glomerular apparatus of the kidneys. These receptors are stimulated by a fall in pressure within the blood vessels entering the glomeruli ,and also by a decrease in the filtration of sodium ions due to a reduced pressure in the glomerular capillaries.

Hypertension:

Systemic arterial hypertension is a major cause of ill health: in the United States, 23 per cent. of the adult population is hypertensive and 65 per cent. of them are either undiagnosed or inadequately treated. Measurement of plasma renin activity in these patients is proving to be of considerable value both for understanding the aetiology of the disease, and also as a guide to the most suitable treatment and to prognosis.

It is convenient to classify hypertensive patients into low, normal and high-renin groups:

Low renin hypertension:

To avoid difficulties due to variations in assay techniques, it is best to ensure that the "low-renin" hypertensive patient is also "suppressed", i.e. that he is unable to respond to a contraction of his extra-cellular fluid (produced by frusemide diuresis) with an increase in his plasma renin activity. Suppression of renin activity shows that renin secretion is being inhibited in an attempt to compensate for the rise in arterial pressure. In the low-renin hypertensive patient, the blood pressure is raised because the kidney is unable to execrete sufficient salt and water; consequently, the extra-cellular fluid volume is expanded and the resulting increase in cardiac output raises the blood pressure. Destruction of kidney tissue is often responsible for salt retention, but it can also result from an excessive secretion of mineralocorticoids, due to a variety of disturbances in adrenal function. 27 per cent. of hypertensive patients without kidney disease have low-renin activity and fall into this category. Their hypertension may be due to a tumour or hyperplasia of aldosterone secreting cells, but many of them fail to show an increase in plasma aldosterone, or the expected fall in serum potassium concentration. Hypertension in these patients is produced by some other mineralocorticoid, probably an oxygenated derivative of 18 HODOC (18 hydroxy, 11 deoxy-corticosterone) which is able to produce renal salt retention without concomitant potassium depletion. The same mineralocorticoid could be reasonable for pregnancy toxaemia, which is another important example of low-renin hypertension not associated with kidney disease. Contrary to earlier reports, low-renin non-renal (i.e. essential) hypertension is *not* more common in the black than in the white population of the United States.

High-renin hypertension:

All hypertensive patients with high renin activity have kidney disease. Rarely, there is a tumour or hyperplasia involving the juxta-glomerular apparatus, but more commonly excessive renin secretion follows obstruction to the renal vascular supply by atheroma or inflammation (glomerulo-nephritis, pyelonephritis). In the accelerated or malignant phase of hypertension, a vicious circle develops: renal vascular narrowing releases renin which causes further spasm, to produce more renin. 16 per cent. of "benign" essential hypertensive patients also have high-renin activity; since their prognosis is decidedly worse, with earlier heart failure and more cerebrovascular accidents, increased renin activity in these patients is probably also due to an extension of arteriolosclerosis into the renal vascular bed.

Normal-renin hypertension:

This is a misnomer: if the arterial pressure is raised, there should normally be a compensatory fall in renin activity; renin activity which would be "normal" in a person with a "normal" blood pressure, is inappropriately high when the blood pressure is raised. "Normal" renin activity increases when the extra-cellular fluid volume is diminished by diuresis, showing that in the normal-renin hypertensive patient, the renin-aldosterone system is attempting to stabalise the blood pressure at a raised and hypertensive level. 57 per cent. of essential hypertensive patients fall into this category and although they may form one extreme of a "normal" biologic variation in arterial blood pressure, their hypertension is a threat to both health and life expectancy: it always requires treatment.

Kidney disease is associated with normal-renin hypertension when salt retention and extra cellular fluid volume expansion are sufficient to suppress and balance increased renin secretion produced by renal vascular damage. Similarly, in patients with aortic coarctation, the low pressure in the renal vascular bed leads to the direct stimulation of renin release which is balanced and suppressed

by the kidneys' inability to excrete salt, and the consequent increase in extra-cellular fluid volume.

Implications:

Although 50-65 per cent. of hypertensive patients have no obvious cause for their disease and are therefore labelled "essential", it is becoming abundantly clear that they do not form an homogenous group; two distinct mechanisms are involved: (1) arteriole narrowing, which by involving the renal vessels leads to the release of renin: high-renin hypertension. These patients require sympatholytic hypotensive therapy (methyldopa, reserpine and propranolol) to lower renin activity by interrupting the sympathetic supply to the kidney; (2) renal retention of salt and water due to an excess of mineralocorticoids with suppression of renin secretion: low-renin hypertension requiring duiretic therapy (hydrochlorothiazide) and aldosterone antagonists (spironolactone).

Comment:

The Medical Professorial Unit at Harare Hospital is at present studying renin secretion in the hypertensive African patient. A comparison with European studies may help to explain why the complications of hypertensive disease show such marked racial differences: coronary thrombosis is virtually restricted to the European hypertensive patient whereas cerebral haemorrhage is equally frequent in the two races, presumably because they both have the same micro-aneurysmal weaknesses in the perforating cerebral arteries. Angiotension (generated by renin) produces heart damage and can explain the more frequent cardiac complications in the European high renin "benign" essential hypertensive patient. Perhaps we shall find that the African patient is relatively renin deficient so that his heart is less susceptible to hypertensive damage. A more likely explanation is that the African's greater tendency to bleed (possibly associated with dietary or pancreatic insulinopaenia) protects him from thrombosis of the coronary arteries but leaves him particularly vulnerable to haemorrhage from cerebral microaneurysms.

Further Reading

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We are pleased to note that Mr. N. G. C. Gane, O.B.E., F.R.C.S.(Ed.), who qualified in April, 1923, at Middlesex Hospital London, has now been registered for 50 years. He has spent almost his entire career in Rhodesia, having joined the Government Service in 1925 in Bulawayo. He then moved to Salisbury the following year as Railway Medical Officer and about three years later joined Mr. Huggins as assistant surgeon in 1929. He became Hon. Senior Surgeon to the Salisbury General Hospital in 1939. In the Second World War he served in the Middle East as a Surgeon Specialist.

On qualifying he was awarded the Lyell Medal and Scholarship for surgery and surgical anatomy. He retired from practice in November 1972.