

WITHDRAWAL OF ENDOGENOUS SYMPATHETIC DRIVE LOWERS BLOOD PRESSURE IN PRIMARY ALDOSTERONISM

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SUMMARY

We were able to observe the effect of withdrawal of endogenous sympathetic drive in a hypertensive patient with an aldosterone-secreting adrenal adenoma. Acute stimulation of both carotid sinus nerves lowered blood pressure to normotensive or hypotensive levels by reducing peripheral resistance. When chronic carotid sinus nerve stimulation was discontinued, peripheral resistance and blood pressure increased. These data suggest that the sympathetic nervous system is important in the maintenance of hypertension in established primary aldosteronism.

The pathogenesis of the hypertension in primary aldosteronism has intrigued and baffled researchers. Whereas there is evidence that the sympathetic nervous system may play a vital role in the development and maintenance of elevated pressures in one animal model of mineralocorticoid hypertension (DOCA-salt hypertension in rats), the possibility that a neurogenic component is important in the hypertension of human primary aldosteronism has received scant study. We had the unique opportunity to document blood pressure and haemodynamic responses to withdrawal of endogenous sympathetic drive in a patient with primary aldosteronism. Our data show that sympathetic drive is not suppressed and suggest that sympathetic nervous activity contributes to the hypertension of primary aldosteronism.

CASE REPORT

The patient, a 47-year-old white male was first observed to have elevated blood pressure (150/90 mm Hg) in 1948 at 16 years of age. Drug treatment was initiated at 34 years when severe hypertension was documented (200/120 mm Hg). Blood pressure control was poor despite multiple therapeutic regimes, and drug-induced side effects were prominent. He complained of intermittent muscle weakness, and hypokalaemia (2.3–3.4 mmol/l) was

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noted on a number of occasions, usually during thiazide treatment. Primary aldosteronism was suspected but plasma renin results obtained in 1972 were difficult to interpret. One renin level was very low, but a second ($397 \text{ ng } 100 \text{ ml}^{-1} \text{ h}^{-1}$) was reported to be within normal limits. The second sample, however, was obtained while the patient's blood pressure was very high (220/140 mm Hg), and the renin-angiotensin system was being stimulated by the combination of a low sodium diet (10 mmol/day), upright body posture, and thiazide and hydralazine treatment. Aldosterone measurements were not obtained at this time.

In view of the uncontrolled hypertension, the drug-related side effects, and in the absence of a definitive diagnosis of primary aldosteronism, consideration was given to attempt blood pressure control with chronic carotid sinus nerve stimulation. The experimental nature of the procedure was fully explained to the patient, and his consent was obtained. Ethical Committee approval was given for this procedure in otherwise uncontrollable hypertension. In February 1972, a Medtronic Barostat® bilateral carotid sinus nerve stimulator was implanted (Schwartz *et al.*, 1967). Over the subsequent 6 years, blood pressure levels were considerably lowered (Fig. 1). Prolonged normalization of pressure was not possible only because the patient experienced an unpleasant sensation in the throat at high baropacer settings, thus diuretic (and supplementary potassium) therapy was required along with a low level of carotid sinus nerve stimulation. Between 1972 and 1978, withdrawal of baropacer stimulation invariably resulted in the return of severe hypertension (Fig. 1). When the baropacer setting was temporarily increased, blood pressure regularly fell to hypotensive levels (less than 110/70 mm Hg, see Fig. 2).

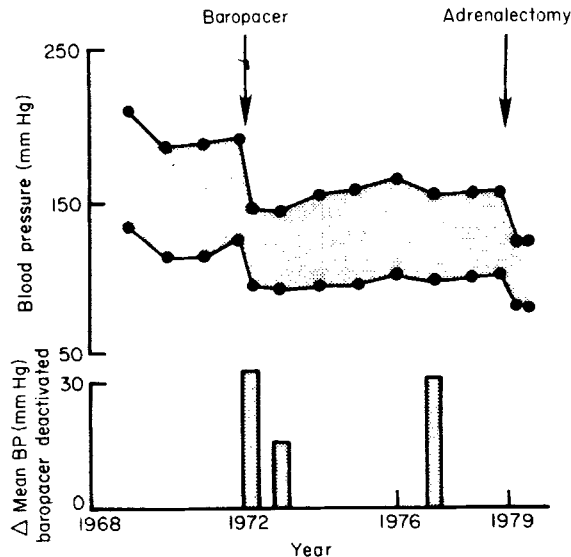


Fig. 1. Blood pressure responses to bilateral carotid nerve stimulation (baropacer), and to unilateral adrenalectomy in a patient with primary aldosteronism. After 1970, blood pressure levels shown are the mean of at least three readings. Multiple combined drug regimes were used prior to baropacer insertion, diuretic and potassium treatment was generally required during the period of baropacer stimulation, and a combination of diuretic and alpha methyl dopa therapy was exhibited after adrenalectomy. The lower panel represents the rise in mean blood pressure when chronic carotid sinus nerve stimulation was temporarily terminated.

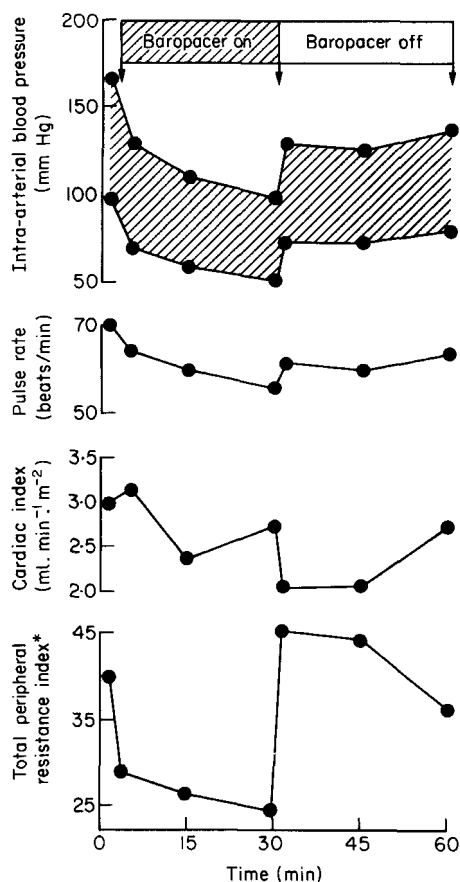


Fig. 2. Haemodynamic responses to bilateral carotid sinus nerve stimulation in a patient with primary aldosteronism during thiazide diuretic and supplemental potassium therapy. The patient was supine during this study. Cardiac output was measured following the injection of indocyanine green. *Resistance index is in arbitrary units (= mean arterial pressure/cardiac index).

Haemodynamic studies performed in 1972 (Fig. 2), and repeated in 1973, showed that baropacer stimulation lowered supine blood pressure primarily by reducing peripheral resistance, although pulse rate and cardiac index also fell somewhat. These changes were reversed when the baropacer was switched off (Fig. 2).

An intermittent electrical malfunction developed from 1975 which necessitated an increase in antihypertensive medication. However, when functioning correctly, baropacer stimulation continued to reduce blood pressure, often to hypotensive levels.

In 1978, the baropacer was switched off, medications were stopped, and treatment with the oral converting enzyme inhibitor captopril (150 mg three times daily) was initiated in the Clinical Research Center at the University of Michigan Hospital. Blood pressure rose to 180/125 mm Hg. Addition of hydrochlorothiazide had little effect on the blood pressure but serum potassium fell to 1.9 mmol/l. The diagnosis of primary aldosteronism was again entertained, and was confirmed when plasma renin activity (Haber *et al.*, 1969) and angiotensin II levels (Nicholls & Espiner, 1976) were found to be low, and serum aldosterone levels (Antunes *et al.*, 1976) did not decline during a high sodium intake

Table 1. Plasma hormone and electrolyte indices (1978)*

	PRA (ng. ml ⁻¹ . h ⁻¹)	Angiotensin II (pg/ml)	Aldosterone (ng/100 ml)	Serum	
				Sodium (mmol/l)	Potassium (mmol/l)
3 days high sodium diet: (Na 200 mmmol/day, K 100 mmol/day)					
Supine	<0.01	<5	36.2	148	2.8
Upright 2 h	<0.01	<5	27.5	142	3.2
Upright 4 h	<0.01	<5	27.6	143	3.1
4 days low sodium diet: (Na 10 mmol/day, K 100 mmol/day)					
Supine	0.08	<5	26.4	145	3.4
Upright 2 h	0.13	<5	27.1	142	3.7
Upright 4 h	0.04	<5	23.7	142	3.7

* The patient was receiving supplemental oral potassium as the only medication for 2 weeks before studies.

Conversion to SI units: PRA 1 ng. ml⁻¹. h⁻¹=0.77 nmol. l⁻¹. h⁻¹. Angiotensin II 1 pg/ml=0.95 pmol/l. Aldosterone 1 ng/100 ml=27.8 pmol/l.

(Table 1). Urine aldosterone excretion (Bayard *et al.*, 1970) measured during the high sodium intake was elevated at 82.5 µg/24 h (normal 2–15 µg/24 h).

Bilateral adrenal vein sampling and venography, together with iodocholesterol adrenal scanning suggested a single adenoma on the left, which was confirmed at unilateral adrenalectomy in January 1979. Two months after surgery urine aldosterone was normal (11.2 µg/24 h), as was his ambulatory plasma renin (2.5 ng. ml.⁻¹ h⁻¹, urine sodium 127 mmol/24 h). Although his blood pressure was slightly elevated at this time (140/88–168/104 mm Hg), it was considerably lower than in previous years (Fig. 1) and was returned to normal by hydrochlorothiazide and α methyl dopa therapy. The patient's vigour and well-being were dramatically improved following unilateral adrenalectomy.

DISCUSSION

The pathogenesis of the hypertension in primary aldosteronism is unclear. It is probable that there is a complex interplay of a number of mechanisms, and that these factors differ in importance at the developmental and the maintenance phases of the hypertension.

Involvement of the sympathetic nervous system in one model of mineralocorticoid hypertension, the DOCA-salt uninephrectomized rat, has been extensively studied. Although interpretation of this literature is open to debate (Louis *et al.*, 1970), the data strongly suggest an important role for the sympathetic nervous system in this type of hypertension. Specifically, studies in this model have documented an increase in norepinephrine turnover in many organs including the heart (de Champlain *et al.*, 1969), raised circulating norpinephrine levels (Reid *et al.*, 1975; de Champlain *et al.*, 1976), enhanced pressor responsiveness to administered norepinephrine (Beilin *et al.*, 1970),

increased sympatho-adrenal activity (Grobeck *et al.*, 1976) and return of blood pressure to normal following either destruction of central catecholergic neurons (Reid *et al.*, 1975) or combined chemical sympathectomy and bilateral adrenalectomy (de Champlain & van Ameringen, 1972).

A possible pathogenic role for the sympathetic system in human mineralocorticoid hypertension has received less attention. During the developmental phase of the hypertension, pulse rate is slowed (Nicholls *et al.*, 1979) and plasma norepinephrine levels fall (Distler *et al.*, 1979), perhaps reflecting a reduction of sympathetic drive at this initial stage. The hypertension of established primary aldosteronism may be hyperkinetic (Tarazi *et al.*, 1973), which would be consistent with there being an active sympathetic nervous system at this phase. On the contrary, there are data suggestive of a reduced adrenergic state in primary aldosteronism (Biglieri & McIlroy, 1966; Distler *et al.*, 1970).

The present case study shows that withdrawal of endogenous sympathetic drive by stimulation of a physiological pathway (the carotid sinus baroreceptor nerves) is capable of returning blood pressure to normal in a patient with established primary aldosteronism. Although anecdotal, this finding has important implications. First, it is evident that unlike the renin-angiotensin system, sympathetic nervous activity was not completely suppressed in our patient. Secondly, in that withdrawal of endogenous sympathetic tone was capable of lowering blood pressure into and below normotensive levels, it is likely that the sympathetic nervous system at least contributed to the maintenance of the hypertension.

The hypertension in established primary aldosteronism is maintained largely by a high peripheral resistance (Tarazi *et al.*, 1973). In the present case, withdrawal of endogenous sympathetic drive returned blood pressure to normal primarily by reducing peripheral resistance. Thus, sympathetic nervous system activity was contributing to the underlying haemodynamic abnormality, i.e. the elevated vascular resistance.

The present data do not allow the conclusion that sympathetic nervous system activity is increased in established primary aldosteronism. Nevertheless, even a 'normal' level of sympathetic function may be important along with other factors, such as hypervolaemia, in determining the degree of hypertension in these patients.

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