Clinical Science (1981) 60, 399–404

Renin and aldosterone release during sympathetic stimulation in tetraplegia

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(Received 6 June/15 September 1980; accepted 20 October 1980)

Summary

1. The effect of endogenous sympathetic stimulation (induced by urinary bladder stimulation) and intravenous infusion of noradrenaline and isoprenaline on blood pressure, heart rate and levels of plasma renin activity and plasma aldosterone were studied in six tetraplegic patients. Data from infusion studies were compared with data from six normal subjects studied in an identical manner.

2. Bladder stimulation in the tetraplegic patients caused a marked rise in blood pressure and fall in heart rate, but no change in plasma renin activity or plasma aldosterone.

3. Noradrenaline infusion resulted in an enhanced pressor response in the tetraplegic patients when compared with the normal subjects. Heart rate fell in both groups. Plasma renin activity and plasma aldosterone did not change in either group.

4. Isoprenaline infusion caused a fall in both systolic and diastolic blood pressure in the tetraplegic patients, unlike the normal subjects in whom there was a rise in systolic and a fall in diastolic blood pressure. Heart rate and plasma renin activity rose in both groups. Plasma aldosterone did not change in either group.

5. We conclude that in tetraplegic patients neither endogenous sympathetic stimulation by bladder stimulation nor infusion of noradrenaline raises plasma renin activity. Isoprenaline increases plasma renin activity to the same extent as in normal subjects. Renin release mechanisms in tetraplegic patients therefore do not appear to be hypersensitive to catecholamines. Plasma aldosterone is not influenced by any of the stimuli.

Key words: aldosterone, isoprenaline, noradrenaline, renin, sympathetic nervous system, tetraplegia, urinary bladder.

Introduction

Tetraplegic patients with physiologically complete spinal cord transection do not appear to have neural connections between the brain and the peripheral sympathetic nervous system. In these patients head-up tilt causes hypotension and little change in levels of plasma catecholamines but a marked increase in plasma renin activity, suggesting that renin release may occur independently of sympathetic activity (Mathias, Christensen, Corbett, Frankel, Goodwin & Peart, 1975). Sympathetic reflexes at a spinal level may, however, be activated in tetraplegic patients by stimulation of the skin and contraction of viscera such as the urinary bladder (Corbett, Frankel & Harris, 1971a) and it is possible that these may either cause or contribute to the rise in plasma renin activity that occurs during head-up tilt. Furthermore even small doses of catecholamines result in enhanced vascular responses in tetraplegics (Mathias, 1976: Mathias, Frankel, Christensen & Spalding, 1976a) and it may be that a small increase in circulating catecholamines during head-up tilt will activate hypersensitive renin releasing mechanisms. We therefore studied the effect of an endogenous increase in sympathetic nervous activity, induced...
by stimulation of the urinary bladder, on levels of plasma renin activity in tetraplegic patients. Plasma renin responses to intravenous infusions of the catecholamines, noradrenaline and isoprenaline were also assessed and compared with normal subjects. Plasma aldosterone levels were measured in an attempt to elucidate the mechanisms of the rise previously reported (Mathias et al., 1975) during head-up tilt.

Subjects and methods

Six tetraplegic patients (five Caucasian males and one Chinese female) with physiologically complete traumatic cervical spinal cord transection between C4 and C8 were studied (Table 1). They were otherwise healthy and were not receiving drugs known to affect autonomic nervous activity. None of the patients had either biochemical or radiological evidence of renal impairment. All had neurogenic bladders and the male patients were on condom drainage; none had indwelling catheters. Six healthy Caucasian subjects (five males and one female) aged between 20 and 32 years were studied as controls. Both patients and control subjects were on unrestricted diets. Informed consent was obtained from all participants. The procedures were approved by the Ethics of Research Committee of Stoke Mandeville Hospital.

All studies were performed in a clinical laboratory. Blood pressure was measured by intra-arterial catheter (by previously described techniques, Mathias et al., 1975) or by mercury sphygmomanometer. Intra-arterial blood pressure recordings were used in all patients in the bladder stimulation study and in one tetraplegic patient during the infusion of noradrenaline and isoprenaline. In the remaining infusion studies, in the patients and control subjects, a sphygmomanometer was used. Heart rate was derived either electronically from the blood pressure signal (when measurements were made by intra-arterial catheter) or from the electrocardiogram (when blood pressure was measured by sphygmomanometer). In the bladder-stimulation studies arterial blood was collected for estimation of plasma renin activity and plasma aldosterone; in the infusion studies in both tetraplegic patients and control subjects blood from a cannula in a forearm vein was used for measurements. Plasma renin activity and plasma aldosterone were measured by radioimmunoassay by previously described techniques (Boyd, Adamson, Fitz & Peart, 1969; James & Wilson, 1976). The inter- and intra-assay coefficients of variation were 7.3 and 4.2% for the renin assay and 11 and 10% for the aldosterone assay.

In the tetraplegic patients the urinary bladder was emptied by suprapubic percussion of the anterior abdominal wall with the fingers before a rest period of 60 min. At the end of this period two basal blood samples 15 min apart were taken. The urinary bladder was then stimulated for approximately 3 min in a manner similar to that described to empty the bladder. Micturition often ensued and the bladder on all occasions was felt to contract. Blood samples were taken at the end of the period of stimulation and 5, 15 and 35 min after cessation of stimulation.

In the drug infusion study, patients and control subjects were rested for a similar period of time (60 min) after emptying the urinary bladder. Noradrenaline was infused in the morning between 10.00 and 11.00 hours and isoprenaline in the afternoon between 13.00 and 14.00 hours. There was an interval of at least 2 weeks between the bladder stimulation and the drug infusion study. Noradrenaline (0.1 μg min⁻¹ kg⁻¹) or isoprenaline (0.01 μg min⁻¹ kg⁻¹) was infused for a period of 10 min by previously described techniques (Mathias et al., 1976a; Mathias, Matthews & Spalding, 1977). Solutions were given within 15 min of preparation. Blood samples were taken at the end of the infusion and 5, 15, 25 and 35 min after its termination.

Student's paired and unpaired t-tests were used to analyse the data. Results were expressed as means ± SEM.
Sympathetic stimuli and renin–aldosterone release

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Bladder stimulation

Bladder stimulation in the tetraplegic patients resulted in a marked rise in both systolic and diastolic blood pressure (from 118 ± 5/60 ± 3 to a maximum of 176 ± 14/82 ± 7 mmHg during stimulation \( P < 0.001 \) and <0.001 respectively) (Fig. 1). Mean heart rate fell from 56 ± 4 to 47 ± 3 beats/min \( P < 0.05 \). Blood pressure and heart rate had virtually returned to basal levels within 10 min of cessation of stimulation. There was no significant change in levels of either plasma renin activity or plasma aldosterone for up to 35 min after stimulation.

Noradrenaline infusion

In the tetraplegic patients infusion of noradrenaline resulted in a substantial rise in blood pressure (Fig. 2) and a fall in heart rate. The pressor response to noradrenaline was significantly greater in the tetraplegic patients when compared with the response in the control subjects (systolic and diastolic pressure increases in the tetraplegic patients were 69 ± 8 and 36 ± 5 mmHg and in the control subjects 23 ± 2 and 19 ± 3 mmHg; \( P < 0.005 \) and <0.025 respectively). In the tetraplegic patients heart rate fell from 64 ± 5 to 48 ± 3 beats/min, whereas in the control subjects heart rate fell from 74 ± 6 to 59 ± 5 beats/min. There was no significant difference in the fall in heart rate between the groups. Levels of plasma renin activity did not change in four out of five tetraplegic patients, either during or after infusion of noradrenaline. In neither the tetraplegic patients nor control group of subjects were there significant changes in mean levels of plasma renin activity or plasma aldosterone, either during or after noradrenaline infusion.

Isoprenaline infusion

In the tetraplegic patients infusion of isoprenaline resulted in a fall in systolic and diastolic blood pressure (Fig. 3). This differed from the control subjects in whom there was an increase in systolic and a decrease in diastolic blood pressure. At the end of infusion only the systolic blood pressure in the tetraplegic patients was lower than in the control subjects \( P < 0.05 \). In the tetraplegic patients during isoprenaline infusion the systolic blood pressure initially fell and then appeared to gradually rise (Fig. 3). After the infusion was stopped both systolic and diastolic blood pressure rose, although only the systolic blood pressure elevation after 25 min reached statistical significance \( P < 0.05 \). During isoprenaline infusion the elevation in heart rate in the tetraplegic patients was not significantly greater than the response in the control subjects. Levels of plasma renin activity (Fig. 3) rose significantly in both groups at the end of the infusion. In the tetraplegic patients mean levels of plasma renin activity rose from 0.79 ± 0.27 to 1.64 ± 0.54 \( P < 0.025 \) and in the control subjects from 0.76 ± 0.18 to 1.34 ± 0.37 pmol h\(^{-1}\) ml\(^{-1}\) \( P < 0.05 \). There was no significant difference between the response in the tetraplegic patients and control subjects.
patients and the control subjects. Plasma aldosterone levels did not change in either group.

Discussion

Stimulation of the urinary bladder in tetraplegic patients with cervical spinal cord transection results in a substantial rise in systolic and diastolic blood pressure and a fall in heart rate (Guttmann & Whitteridge, 1947). Physiological studies indicate that reflex vasoconstriction occurs in vessels in forearm and calf muscles and this is thought to be due to increased sympathetic nervous activity occurring via the isolated spinal cord (Corbett et al., 1971a). Biochemical evidence to support this had been obtained from levels of plasma noradrenaline and plasma dopamine β-hydroxylase, which rise during such induced hypertension (Mathias, Christensen, Corbett, Frankel & Spalding, 1976c; Mathias, Smith, Frankel & Spalding, 1976b). Although levels of plasma noradrenaline increase threefold during bladder stimulation, no change in plasma adrenaline levels has been detected (Mathias et al., 1976c). In the tetraplegic patients during and after such endogenous sympathetic stimulation there were no changes in levels of plasma renin activity. Nanniga, Rosen & Krumlovsky (1976) also observed no change in renin levels in tetraplegic patients during hypertension induced by bladder distension. These workers, however, did not provide details either of the level of completeness of the lesion in their patients or of the method of measurement of renin. The two independent studies, however, indicate that spinal reflex sympathetic activity does not appear to raise plasma renin activity levels in tetraplegic patients. There remains the theoretical possibility of selective sparing of the renal vascular bed during the provoked sympathetic outburst, but this seems unlikely in view of the evidence of widespread vascular reactivity.

Intravenous infusion of noradrenaline resulted in a marked pressor response in the tetraplegic patients that was greater than in the control subjects. Infusion of noradrenaline did not raise levels of plasma renin activity in either of the two groups. Hypersensitivity of renin-releasing mechanisms to noradrenaline therefore does not occur in the tetraplegic patients and it is most unlikely, therefore, that the small rise in noradrenaline during head-up tilt in these patients (Mathias et al., 1975) contributed directly to the rise in plasma renin that has been observed by previous workers (Johnson, Park & Frankel, 1971; Mathias et al., 1975).
accumulating experimental evidence that α-adrenoreceptor stimulation impairs renin release (Pettinger, Keeton, Campbell & Harper, 1976; Vandongen & Peart, 1974; Vandongen, Strang, Poesse & Birkenhager, 1979), which is in accord with observations in normal subjects given either α-adrenoreceptor antagonists or agonists (Hsu et al., 1977). It is, therefore, not surprising that bladder stimulation, which appears to result in largely α-adrenoreceptor stimulation, does not cause the release of renin. There is animal evidence that stimulation of renal nerves releases renin probably via sympathetic fibres; the inhibition of release by propranolol favours its dependence on renal β-adrenoreceptor stimulation (Lagrange, Sloop & Schmid, 1973; Zanchetti & Stella, 1975). In the isolated perfused kidney small doses of noradrenaline make it a potent renin releaser because of its β-adrenoceptor effect while as the dose is increased, the α-adrenoceptor effect ascends and renin release is reduced (Vandongen & Greenwood, 1975). It may be that in the tetraplegic patients during bladder stimulation the α-adrenoceptor effects are predominant and thus inhibit the normal β-adrenoceptor-mediated release of renin.

In normal man intravenous infusion of isoprenaline results in a dose-related rise in levels of plasma renin activity (Johnson, Smith, Labrooy & Bye, 1976a; Davies, Slater, Rudolph & Geddes, 1977; Harms, Gooren, Spoelstra, Hesse & Verschoor, 1978). In both tetraplegic patients and control subjects isoprenaline produced a twofold elevation in levels of plasma renin activity. In animals isoprenaline is thought to release renin by an action mainly on intrarenal β-adrenoreceptors (Johnson, Davis, Gotshall, Lohmeier, Davis, Braverman & Tempel, 1976b), but it may be that the vasodilatation induced by β-adrenoceptor stimulation also plays a role. Whether either or both mechanisms contribute to the release of renin in man is unclear. During infusion of isoprenaline the diastolic blood pressure in the tetraplegic patients fell to a level similar to that in the control subjects. There was, however, no rise in systolic blood pressure and the reason for this is not clear. It may reflect the inability of tetraplegic patients reflexly to increase sympathetic nervous activity during vasodilatation, as would be expected to occur in normal man. After infusion of isoprenaline in the tetraplegic patients there was a blood pressure overshoot that also occurs in these patients on return to the horizontal after head-up tilt (Corbett, Frankel & Harris, 1971b). Corbett et al. (1971b) postulated that bladder distension and increased sympathetic activity accounted for the blood pressure change whereas Johnson et al. (1971) favoured a role for the renin–angiotensin system in this response. It is possible that a rise in circulating levels of angiotensin II, secondary to the increase in plasma renin activity, contributes to the blood pressure overshoot after both head-up tilt and isoprenaline infusion.

In our studies none of the stimuli changed circulating levels of aldosterone in either the tetraplegic patients or the control subjects. In tetraplegic patients head-up tilt causes a marked rise in plasma aldosterone levels which occurs after the elevation of plasma renin activity (Mathias et al., 1975). It is not clear if this is due to the adrenal stimulant effect of increased levels of angiotensin II (Laragh, Angers, Kelly & Lieberman, 1960), to a decrease in splanchnic blood flow altering the metabolic clearance of aldosterone (Davis, 1972) or to the inhibition of release renin-releasing mechanisms (Mathias et al., 1975). The possibility of hypersensitive angiotensin II adrenal receptors seems unlikely.

We conclude that in tetraplegic patients levels of plasma renin activity do not change during endogenous sympathetic stimulation induced by activation of the urinary bladder. There is no evidence of hypersensitivity of renin-releasing mechanisms to circulating noradrenaline. Levels of plasma renin activity rise to a similar extent in both tetraplegic patients and control subjects during infusion of isoprenaline. This effect may be due to direct stimulation of intrarenal β-adrenoreceptors, to renal baroreceptor stimulation induced by β-adrenoreceptor induced vasodilatation or to a combination of the two mechanisms.

Acknowledgments

We thank Mrs J. Dulieu, Miss F. Pike, Mrs P. Smith and Mr G. Wilson for technical assistance, Miss Angela Hill and Miss Anne O’Hanlon for secretarial help and Dr J. M. K. Spalding for valuable advice. C.J.M. is a Wellcome Senior Research Fellow in Clinical Science and I.B.D. is a Ciba Research Fellow.
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