Plasma catecholamines, plasma renin activity and plasma aldosterone in tetraplegic man, horizontal and tilted

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Summary

1. Plasma catecholamines, plasma renin activity, plasma aldosterone and haematocrit were measured in four subjects with physiologically complete cervical spinal cord transections, before, during and after head-up tilt to 45° for 30 min. Plasma catecholamines were measured in five normal male volunteers in the supine position and after head-up tilt to 45° for 10 min.

2. After 10 min of head-up tilt, the plasma noradrenaline rose 14% in the tetraplegic patients and 115% in the control subjects. These findings indicate a failure of sympathetic activity in response to head-up tilt in the tetraplegic patients, probably caused by interruption of pathways by which the brain normally controls sympathetic outflow.

3. In the tetraplegic patients the resting plasma renin activities were above normal, and rose more quickly and greater on head-up tilt than in published studies of normal subjects. It is likely that the renal baroreceptors are important in the control of renin release.

4. In the tetraplegic patients, there was a late rise in plasma aldosterone which was probably due to the elevation in plasma renin activity.

Key words: aldosterone, angiotensin, catecholamines, posture, renin, tetraplegia.

Introduction

Patients who are tetraplegic from acute cervical spinal cord transections at first have severe hypotension if tilted head-up (Walsh, 1960). Regular and frequent postural changes help in gradually overcoming this hypotension (Guttmann, 1973). The mechanism of this improvement is not known. It has been suggested that sympathetic activity or the renin-angiotensin system may play a part (Corbett, Frankel & Harris, 1971; Johnson, Park & Frankel, 1971). The present investigations were designed to elucidate this problem.

Methods

Subjects

Four patients with traumatic cervical spinal cord lesions were examined (Table 1). The lesions were physiologically complete, with complete chronic loss of sensation and voluntary motor power in parts of the body innervated from below the level of the cord transection. There is normally no sympathetic outflow above the first dorsal spinal segment (Truex & Carpenter, 1969) so that,
in these patients, the brain could not control the sympathetic outflow from the spinal cord. None of the patients was bedridden and all were active in their wheelchairs. All were on unrestricted diets. They had received no drugs for at least 24 h before the study. None had any disease, including renal disease, which was likely to affect the results.

Blood urea and plasma creatinine values were normal. All patients volunteered after being told the nature and purpose of the study. Some had either co-operated in or witnessed similar investigations previously. Five healthy males aged 26, 33, 34, 39 and 39 years were also examined to determine the effect of head-up tilt on concentrations of plasma catecholamines. None was on drug therapy, and all volunteered for the investigations, which had been approved by the Ethics Committee of the Hospital.

**Procedure**

The patients were investigated in the supine position and during head-up tilting. The patient was brought from the ward on his bed and transferred to an electrical tilting bed (Rank Precision Industries Ltd, London). Care was taken to see that no undue movement or spasm was caused. Before the commencement of the study, a pair of specially modified trousers was attached by stout straps to suspension points on top of the bed frame. The patient was tilted smoothly at a rate of approximately 3°/s from the horizontal to 45° head-up, remained there for 30 min, and was then returned to the horizontal.

Blood pressure and heart rate were continuously recorded and the electrocardiograph was displayed continuously. Plasma noradrenaline, plasma adrenaline, plasma renin activity, plasma aldosterone and the haematocrit were measured in the horizontal position, during head-up tilt to 45° for 30 min, and after return to the horizontal position. In the healthy subjects, plasma noradrenaline and plasma adrenaline were measured in the horizontal position and after 45° head-up tilt for 10 min.

A polytetrafluoroethylene (Teflon) cannula was introduced with an aseptic percutaneous technique into either the dorsalis pedis or femoral artery. This was connected via tubing filled with sodium chloride solution (150 mmol/l; saline) to an electromanometer mounted so that throughout the investigations it remained level with the fourth intercostal space, just anterior to the mid-axillary line (Winsor & Burch, 1946). The electromanometer was fixed to the moving part of the bed frame so that its position altered with that of the patient. Between the cannula and the electromanometer was a device (MacMillan & Stott, 1968) which provided both continuous perfusion of the cannula with sterile saline and series mechanical damping of the arterial pressure system by an adjustable stenosis. The blood pressure signal was used to trigger a beat-to-beat heart-rate meter (Nielson, type 2750, Devices Instruments Ltd), so that instantaneous heart rate was derived. These signals were amplified and recorded on a four-channel rectilinear pen recorder (Devices M4, Welwyn Garden City, Herts.). The arterial line had a three-way connector which facilitated the withdrawal of blood samples. Precautions were taken to ensure that the sample was free of saline.

**Assay methods**

Blood for catecholamine measurement was immediately transferred to ice-cooled tubes containing ascorbic acid and ethylenediamine tetra-acetic acid (EDTA), 2 mg of each per ml of whole blood. The plasma was separated by centrifugation at 4°C and was frozen at -20°C. Plasma noradrenaline and adrenaline were determined by the modified (Christensen, 1973) double-isotope technique of Engelman & Portnoy (1970). The lowest value of plasma adrenaline detectable with this assay is approximately 0·05 pmol/ml (0·01 ng/ml) in 5–10 ml of plasma. In the control subjects, plasma catecholamines were measured in venous blood with an identical method. Previous studies have shown that the plasma catecholamine concentration is the same in venous and arterial blood (Christensen & Brandsborg, 1973; Christensen & Videbaek, 1974).

Plasma renin activity was measured in arterial blood samples by the radioimmunoassay method of Boyd, Adamson, Fitz & Peart (1969). Arterial blood was collected in disposable plastic syringes containing 0·6 ml of freshly mixed Dimercaprol (Sigma Laboratories; 200 mmol/l) and 1·0 ml of EDTA (0·3 mol/l; pH 7·5), which were used to inhibit 'angiotensinases' and plasma converting-enzyme activities (Boyd, Landon & Peart, 1967; Ryan, McKenzie & Lee, 1968). The samples were immediately transferred to ice-cooled polyethylene
Hormones and posture in tetraplegia

TABLE 1. Details of tetraplegic patients and mean blood pressure and heart rate before, during and after head-up tilt to 45°

In calculating changes in MBP and HR, the resting value is taken as the mean of the values 30 min (−30) before, and immediately (0) before, tilting. MBP = mean blood pressure; HR = heart rate.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years) and sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Spinal level of lesion</th>
<th>Time since lesion (months)</th>
<th>Resting MBP (mmHg)</th>
<th>Head-up tilt MBP (mmHg)</th>
<th>Horizontal MBP (mmHg)</th>
<th>Resting HR (beats/min)</th>
<th>Head-up tilt HR (beats/min)</th>
<th>Horizontal HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19 M</td>
<td>173</td>
<td>70</td>
<td>C6</td>
<td>6</td>
<td>85</td>
<td>89</td>
<td>67</td>
<td>67</td>
<td>81</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>25 M</td>
<td>183</td>
<td>76.4</td>
<td>C6</td>
<td>3</td>
<td>77</td>
<td>79</td>
<td>30</td>
<td>55</td>
<td>62</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>32 M</td>
<td>168</td>
<td>83.6</td>
<td>C3/C4</td>
<td>8</td>
<td>75</td>
<td>73</td>
<td>38</td>
<td>63</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>42 F</td>
<td>152</td>
<td>46.4</td>
<td>C6</td>
<td>62</td>
<td>87</td>
<td>80</td>
<td>73</td>
<td>83</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>Mean</td>
<td>30</td>
<td>169</td>
<td>69.1</td>
<td></td>
<td>20</td>
<td>81</td>
<td>80</td>
<td>72</td>
<td>71</td>
<td>62</td>
<td>80</td>
</tr>
</tbody>
</table>

tubes and centrifuged at 4°C. Duplicate 10 ml portions were extracted both at zero time and after incubation at 37°C for 4 h. Angiotensin I was extracted from each batch of plasma and estimated by the radioimmunoassay method.

Arterial blood samples for plasma aldosterone were simultaneously collected, placed in ice-cooled lithium-heparin tubes, and immediately centrifuged at 4°C. Plasma aldosterone was measured by the radioimmunoassay method of Mayes, Furuyama, Kem & Nugent (1970).

Arterial haematocrit was measured with a Coulter counter (model S, Coulter Electronics Ltd).

The plasma catecholamine results were statistically analysed by the use of t-tests and paired t-tests.

Results

Blood pressure and heart rate

All tetraplegic patients had a fall in systolic, diastolic and mean blood pressure during tilting. In patient no. 2, the MBP fell as low as 30 mmHg, and in patient no. 4 only to 73 mmHg (Table 1). Patients no. 2 and no. 3 felt faint for a short interval during the period of head-up tilt. After 10 min tilting, the average MBP had dropped by 36%; at 30 min it had dropped by 25%. All tetraplegic patients had increases in heart rate during some stage of head-up tilting. Patient no. 4, who did not have a significant fall in MBP, had the smallest change in heart rate during tilting. The mean maximum increase in heart rate was 21%, the mean increase at 10 min was 12%, and at 30 min it was 21%.

Plasma catecholamines

The mean resting concentration of plasma noradrenaline was 0.74 pmol/ml (0.13 ng/ml) in the control subjects, and 0.40 pmol/ml (0.07 ng/ml) in the tetraplegic patients (Table 2), a significant difference (P < 0.02). The mean basal plasma adrenaline concentration was 0.14 and 0.08 pmol/ml (0.03 and 0.02 ng/ml) respectively, and there was no significant difference. Ten minutes after tilting, the plasma noradrenaline in the control subjects rose to 1.68 pmol/ml (0.28 ng/ml) (P < 0.001). The plasma adrenaline rose to 0.24 pmol/ml (0.04 ng/ml) (P < 0.05). In the tetraplegic patients the plasma noradrenaline and plasma adrenaline concentrations were almost unchanged 10 min after tilting and both mean values were significantly lower than the corresponding 10 min values obtained in the control subjects (P < 0.002, 0.01). Twenty minutes after tilting, the plasma noradrenaline in the tetraplegic patients had increased to 0.67 pmol/ml (0.11 ng/ml) (P < 0.05), and to 0.75 pmol/ml (0.13 ng/ml) at 30 min (P < 0.05). The plasma nor-
TABLE 2. Plasma noradrenaline and adrenaline in four tetraplegic subjects at rest, 10, 20 and 30 min after 45° head-up tilt, and 75 min after the start of head-up tilt, when they had been horizontal again for 45 min

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Resting</th>
<th>Head-up tilting</th>
<th>Horizontal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 min</td>
<td>20 min</td>
</tr>
<tr>
<td>Plasma noradrenaline (pmol/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.53</td>
<td>0.24</td>
<td>0.83</td>
</tr>
<tr>
<td>2</td>
<td>0.35</td>
<td>0.71</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0.41</td>
<td>0.53</td>
<td>0.59</td>
</tr>
<tr>
<td>4</td>
<td>0.30</td>
<td>0.47</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.40</td>
<td>0.49</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>± 0.10</td>
<td>± 0.19</td>
<td>± 0.14</td>
</tr>
<tr>
<td>Plasma adrenaline (pmol/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.05</td>
<td>0.16</td>
<td>0.00</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>3</td>
<td>0.16</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.08</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>± 0.06</td>
<td>± 0.08</td>
<td>± 0.03</td>
</tr>
</tbody>
</table>

FIG. 1. Plasma renin activity in four tetraplegic subjects (▲, ■, ○, □, nos. 1–4 respectively), 30 min before, and 0, 10, 20 and 30 min after 45° head-up tilt, and 45 and 75 min after the start of head-up tilt, when they had been horizontal again for 15 and 45 min. In calculating changes in plasma renin activity the resting value is taken as the mean of the values 30 min (−30) before and immediately (0) before tilting. The unbroken line represents mean values for the four patients.
adrenaline was elevated after the patients had been horizontal for 45 min (Table 2).

**Plasma renin activity**

Resting PRA values in the patients were 1.4, 4.3, 2.47 and 0.74 pmol h⁻¹ ml⁻¹, with a mean value of 2.23 pmol h⁻¹ ml⁻¹ (1544, 4731, 2712 and 818 pg h⁻¹ ml⁻¹, mean 2451 pg h⁻¹ ml⁻¹) (Fig. 1). This is higher than normal resting PRA values measured in our laboratory, which are between 0.06 and 0.49 pmol h⁻¹ ml⁻¹ (65-540 pg h⁻¹ ml⁻¹) in recumbent resting normal subjects on unrestricted diets (Boyd et al., 1969). During tilt, the maximum mean PRA was 11.50 pmol h⁻¹ ml⁻¹ with a mean maximum increase of 416% (range 101-722%). Patient no. 4, who had a negligible pressure drop, had the least increase in PRA. The mean increase in PRA after 10 min of tilt was 213% (range 49-296%), after 20 min it was 347% (range 79-722%), and after 30 min, 340% (range 101-436%).

**Plasma aldosterone**

The resting concentrations of plasma aldosterone in the tetraplegic patients were 308, 182, 210 and 210 pmol/l, with a mean value of 228 pmol/l (11, 6.5, 7.5 and 7.5 ng/100 ml respectively, mean 8 ng/100 ml) (Fig. 2). These are within or close to the normal limits of 56-280 pmol/l (2-10 ng/100 ml) (Mayes et al., 1970). During tilting, there was a significant increase in these values to a mean of 700 pmol/l (25 ng/100 ml), with a mean maximum increase of 207% (range 87-254%). After 10 min of tilt, the mean change was an increase of 14% (range -33-85%). After 20 min the mean increase
was 88% (range 27-193%) and after 30 min it was 161% (range 87-254%).

**Haematocrit**

The haematocrit was estimated in the patients at intervals before, during and after tilting to ascertain changes in haemodilution. There were no significant changes during the study.

**Discussion**

Passive head-up tilting of a normal subject to between 40° and 60° causes insignificant changes in systolic blood pressure, a slight elevation of diastolic blood pressure, a minimal increase in MBP, and a significant increase in heart rate (Tuckman & Shillingford, 1966; Frohlich, Tarazi, Ulrych, Dustan & Page, 1967; Molzahn, Dissmann, Halim, Lohmann & Oelkers, 1972). Tilting of tetraplegic man causes a fall in systolic, diastolic and mean blood pressure and an increase in heart rate (Guttmann, Munro, Robinson & Walsh, 1963). Extreme degrees of hypotension, some without loss of consciousness, have been reported (Corbett et al., 1971). Prolonged bed rest of 2-3 weeks in normal man does not generally influence the blood pressure response to head-up tilting, though exaggerated increases in heart rate may occur (Chobanian, Lille, Tercyak & Blevins, 1974). A fall in blood pressure (Miller, Johnson & Lamb, 1964) and vasodepressor reactions may occur in a few apparently normal individuals during head-up tilt (Chobanian et al., 1974). In tetraplegic man, however, the effect of prolonged recumbency is unlikely to be important, for the orthostatic hypotension is more severe and more consistent than in normal man after prolonged bed rest, and it develops immediately if the cervical cord lesion is acute. The patients studied were, moreover, accustomed to being in wheelchairs much of the day.

The catecholamine response to posture in normal man was observed initially by von Euler, Luft & Sundin (1955), who reported an increased urinary output of noradrenaline during tilting, and suggested that this was due to reflex sympathetic activity. Moreover, increases in plasma noradrenaline in normal subjects during head-up tilt have also been observed (Hickler, Hamlin & Wells, 1959; Molzahn et al., 1972; Fluck & Salter, 1973). Changes in plasma concentrations of catecholamines have been studied in tetraplegic patients by Guttmann et al. (1963), who reported lower resting concentrations of catecholamines and less increase on head-up tilt in them than in normal subjects. These studies had methodological limitations and the present method of estimation of plasma catecholamines is more sensitive and specific, especially at lower catecholamine concentrations (Christensen, 1972). The low resting concentrations of plasma noradrenaline and plasma adrenaline in our tetraplegic subjects confirm previous work on similar patients using identical methods (Debeuge, Christensen, Corbett, Eidelman, Frankel & Mathias, 1974). The increase in plasma noradrenaline on head-up tilt in normal subjects is likely to be due mainly to noradrenaline release from sympathetic nerve endings. In our tetraplegic patients the increase was very much smaller, i.e. 14% compared with 115% in the control subjects after 10 min of head-up tilting to 45°. This may be due to failure of sympathetic activity in the tetraplegic patients because the sympathetic outflow is cut off from control by the brain. A greater rise in plasma adrenaline than plasma noradrenaline has been reported as the cause of fainting in tetraplegic and paraplegic patients when tilted head-up (Guttmann et al., 1963). We have been unable to confirm these findings, for the plasma adrenaline did not rise on head-up tilt in the two tetraplegic patients (no. 2 and no. 3) who felt faint.

Plasma aldosterone in the resting tetraplegic patients was close to the upper limit of normal (56–280 pmol/l, Mayes et al., 1970). With head-up tilt it rose to 700 pmol/l (mean), comparable with the rise occurring in normal man (Balikian, Brodie, Dale, Melby & Tait, 1968). These findings contrast with reports of subnormal aldosterone excretion in patients with orthostatic hypotension due to autonomic insufficiency. Of these, one patient had amyloidosis (Gordon, Küchel, Liddle & Island, 1967), and four in another series of five had other pathology (Slaton & Biglieri, 1967). There have, however, been reports of normal aldosterone secretory rates in patients with the Shy–Drager syndrome (in whom anhidrosis, sexual impotence and orthostatic hypotension occur due to autonomic failure) (Chokroverthy, Barron, Katz, del Greco & Sharp, 1969). Renin gives rise to angiotensin II, which stimulates production of aldosterone (Genest, Nowaczynski, Korn, Sander & Biron, 1960; Laragh, Angers, Kelly & Lieberman, 1960), and changes in PRA in most situations correlate with
changes in plasma aldosterone (Michelakis & Horton, 1970). The rise of plasma aldosterone in our tetraplegic patients during head-up tilt was slightly later than, and could be a consequence of, the rise in PRA, though altered splanchnic blood flow and a reduction in the metabolic clearance rate of aldosterone (Davis, 1972; Weidmann, Horton, Maxwell, Franklin & Fichman, 1973) should be considered.

In the normal subject, with identical methods, the mean resting PRA is $0.20 \text{ pmol h}^{-1} \text{ ml}^{-1}$ (Boyd et al., 1969). In the tetraplegic subjects, the mean resting PRA was much above normal ($2.23 \text{ pmol h}^{-1} \text{ ml}^{-1}$). With head-up tilt, the mean PRA rose 213% within 10 min, reached 347% in 20 min, and was 340% in 30 min. An increase in PRA occurs in normal subjects on unrestricted diets during upright posture (Nielson & Møller, 1968). In this study PRA was measured by a bioassay method and hence only percentage increases are mentioned for comparison. The mean PRA rose 21% in 10 min, was 132% in 20 min, and reached 144% in 40 min. The PRA in our tetraplegic subjects was therefore much higher than normal at rest, and the rise may be quicker and higher on head-up tilt. This supports previous findings of a raised PRA (Mendelsohn & Johnston, 1971), and plasma renin concentration (Johnson et al., 1971) in tetraplegic patients, and of an exaggerated response to head-up tilt.

Renin release in these subjects could have been due to activity either of the sympathetic nervous system or renal baroreceptors. There is evidence that the sympathetic nervous system is implicated in renin release, both in animals (Vander, 1967; Ueda, Yasuda, Takabataka, Iizuka, Iizuka, Ihori & Sakamoto, 1970; Loeffler, Stockigt & Ganong, 1972; Vandongen, Peart & Boyd, 1973) and in man (Gordon et al., 1967; Chokroverthly et al., 1969; Winer, Choksi, Yoon & Friedman, 1969). Patients with autonomic insufficiency have been examined to determine whether PRA alters when they are tilted head-up. Some authors have found that it does not. One of these patients, however, did not have sufficient orthostatic hypotension to faint when vertical (Gordon et al., 1967), two of the patients in another series, with the Shy–Drager syndrome, were tilted for only 2–3 min (Chokroverthly et al., 1969), whereas in the other patients the published data do not indicate clearly the extent of autonomic involvement (Bozovic, Castenfors & Orö, 1970). Other authors, however, have found that PRA rises during head-up tilt in patients with autonomic insufficiency and the Shy–Drager syndrome (Hedeland, Dymling & Hökfelt, 1969; Bliddal & Nielson, 1970; Diamond, Murray & Schmid, 1970). It has been suggested that certain components of efferent sympathetic pathways may be important for renin release, but that it is not necessary that afferent parts of autonomic reflexes should be intact (Love, Brown, Chinn, Johnson, Lever, Park & Robertson, 1971). In that paper, however, the patients described on the basis of physiological tests as having afferent lesions had the Holmes–Adie syndrome, and this is itself evidence of an efferent lesion (Ruttner, 1947; Harriman & Garland, 1968). In our tetraplegic patients, resting PRA was high, and in patients no. 1, no. 2 and no. 3, tilting head-up was followed by an increase in PRA which was probably more rapid and greater than occurs in normal subjects. The amount of sympathetic activity may be gauged from the plasma noradrenaline concentrations. Unless it is postulated that the renin-release mechanisms are hypersensitive to noradrenaline and that there are baroreceptors with afferents leading to the isolated part of the spinal cord, the poor response of plasma noradrenaline to tilting suggests that in the tetraplegic patients the rise in PRA was not primarily due to sympathetic activity.

Alternatively, the renin release could be due to renal baroreceptors. Their involvement in renin release has long been postulated by several investigators (Braun-Menendez, Fasciolo, Leloir, Munoz & Taquini, 1946). It has been suggested that the juxtaglomerular granular cells in the media of the afferent arterioles act as stretch receptors (Tobian, 1962). Reduction in mean renal perfusion pressure in dogs causes an increase in renin secretion (Skinner, McCubbin & Page, 1964; Blaine & Davis, 1971). Arterial hypotension may produce autoregulatory dilatation in afferent arterioles, and in animals this is accompanied by renin release (Eide, Lønning & Kill, 1973). In our tetraplegic patients no. 1, no. 2 and no. 3, the average MBP fell on head-up tilt from 83 to 40 mmHg (52%), a substantial stimulus to baroreceptor mechanisms. In these tetraplegic patients there was a marked rise in PRA. In patient no. 4, however, the mean blood pressure fell on head-up tilt only from 84 to 73 mmHg, (13%), a minimal stimulus to baroreceptor mechanisms, and in her there was the least rise in PRA.
Acknowledgments

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References


