PLASMA CATECHOLAMINES IN TETRAPLEGICS

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INTRODUCTION

BLADDER and muscle stimulation are known to cause cardiovascular changes in tetraplegics (Head & Riddoch, 1917; Riddoch & Head, 1917; Guttman & Whitteridge, 1947; Cunningham *et al.*, 1953; Kurnick, 1956; Roussan *et al.*, 1966; Corbett *et al.*, 1971a and b). Bladder stimulation causes a rise in arterial mean blood pressure and pulse pressure with a decreased heart rate, decrease in calf and hand blood flow and venoconstriction. These occur whether the bladder is full or empty and whether intravesical pressure has risen or not. Muscle stimulation and skeletal muscle spasm causes similar changes which are independent of bladder pressure changes (Corbett *et al.*, 1971a). Recent experiments conducted in this hospital have also indicated an increase in cardiac output, stroke volume and calculated systemic vascular resistance during suprapubic percussion and bladder stimulation and during skeletal muscle spasm (Debarge, 1973).

Present observations were conducted to correlate plasma catecholamine changes with cardiovascular responses, in particular to alterations in blood pressure.

SUBJECTS

Two female and four male afebrile patients aged between 18 and 40 years (average 28 years) were examined. All had localised traumatic cervical spinal cord lesions at C6 and C7 which were physiologically complete and had occurred 7 to 168 months previously (average 72 months). No patient was bedridden and all were used to moving around in their wheelchairs. Some of the patients were on drug therapy, but all drugs were discontinued 24 hours before observations were made. Their weight ranged between 48 and 73 kg. (average 58 kg.), height between 150 and 183 cm. (average 171 cm.). None was suffering from any constitutional disease or complication which could have affected the results. All patients volunteered freely after being told the nature and purpose of the investigation and some had witnessed or cooperated in similar investigations previously. Two normal male subjects aged 21 and 22 years respectively, also volunteered freely and observations on them were also made.

METHODS

All patients were investigated in the supine position. An intra-arterial polytetrafluorethylene (Teflon) catheter was introduced percutaneously into the radial, femoral or dorsalis pedis artery. This was connected via a saline-filled

catheter to an electromanometer mounted so that throughout the investigation it remained level with the fourth intercostal space just anterior to the mid-axillary line. The blood pressure signal was also used to trigger a beat-to-beat heart rate meter and thus instantaneous heart rate was derived from the blood pressure trace. These signals were amplified and recorded on a rectilinear pen recorder. The arterial line had a three-way connector to facilitate the withdrawal of blood samples for plasma catecholamine estimation.

Bladder percussion was effected by percussing the bladder through the anterior abdominal wall. Four patients were studied and seven estimations were done of plasma catecholamines and on the cardiovascular changes which accompany bladder stimulation.

Muscle stimulation was produced with an electrical muscle stimulator. To prevent damage to the skin the position of the electrodes on the skin was varied frequently. The bladder was emptied at least 30 minutes prior to muscle stimulation and prior to getting basal values. Seven estimations were conducted on six patients in whom skeletal muscle spasms were caused by muscle stimulation.

Noradrenaline was infused at a constant rate of 8 micrograms per minute (except in one case where it was 4 micrograms per minute) into a Teflon catheter situated in a peripheral vein for periods ranging from 3.5 to 11 minutes. In five patients changes in blood pressure and heart rate were recorded and blood samples were taken for plasma catecholamine estimation before infusion and when the blood pressure was at its highest.

Samples for catecholamine estimation were withdrawn through the intra-arterial cannula. Blood was taken during the basal state at 1.5 to 2.5 minutes after either bladder percussion or muscle stimulation. During noradrenaline infusion blood was taken at the height of the pressor response. After this the infusion was stopped. Blood was immediately transferred to ice cold tubes containing ascorbic acid and ethylene diamine tetra-acetic acid, 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 estimated by the double isotope technique (Engelman *et al.*, 1968; Engelman and Portnoy, 1970; Christensen, 1972). The standard deviation of the single determination for samples containing 0.8 ng. per ml. of noradrenaline was ± 0.03 or 4 per cent. (Videbaek *et al.*, 1972). Storing the plasma at -20°C. for up to 3 weeks has shown very similar values for noradrenaline and slightly higher values at the second estimation for adrenaline (Christensen, 1972).

The two normal male subjects received infusions of noradrenaline and their blood pressure was measured as described earlier.

RESULTS

Bladder Stimulation. The cardiovascular effects and plasma catecholamine changes following bladder percussion and stimulation were observed in four subjects in whom seven estimations and observations were made. There was a consistent blood pressure rise in all subjects of both systolic and diastolic blood pressure (fig. 1, A), and these changes were always accompanied by a fall in heart rate. Mean blood pressure rose by an average of 75 per cent. while the heart rate fell by an average of 20 per cent. Resting levels of noradrenaline and adrenaline were lower than normal. The normal levels of plasma noradrenaline

FIG. 1

Blood pressure and plasma noradrenaline and adrenaline levels before (at left) and during (at right) bladder percussion (a), muscle stimulation (b) and infusion of noradrenaline (c), in subjects with physiologically complete cervical cord lesions.

FIG. 2

Percentage change in mean blood pressure during noradrenaline infusion in normal controls and in tetraplegic subjects with physiologically complete cervical cord lesions. The rate of infusion in each subject is given in $\mu\text{g./kg./min.}$ above each block.

are 0.22 ng. per ml. with an S.D. of ± 0.09 and the levels of plasma adrenaline are 0.05 ng. per ml. with an S.D. of ± 0.05 (Christensen, 1972). These are plasma catecholamine levels in 16 normal subjects resting in the supine position with an average pulse rate of 70, S.D. ± 11 , and an average blood pressure of 134/86, S.D. $\pm 26/12$. No sex difference was found. The average basal noradrenaline levels in the tetraplegics was 0.04 ng. per ml., while the basal adrenaline levels were 0.00 ng. per ml. These rose to 0.19 and 0.04 ng. per ml. respectively on bladder stimulation.

Muscle Stimulation. Muscle stimulation produced similar though less marked cardiovascular changes (fig. 1, B). The mean blood pressure rose by an average of 37 per cent. while the heart rate fell by an average of 9 per cent. The average basal plasma noradrenaline levels were 0.07 ng. per ml. while the average adrenaline levels were 0.00 ng. per ml. These rose to an average of 0.23 and 0.03 ng. per ml. respectively on muscle stimulation.

Noradrenaline Infusion. An infusion of noradrenaline intravenously was made to assess the effect of circulating catecholamines on the cardiovascular system. In the tetraplegic subjects there was an increase in systolic and diastolic blood pressure (fig. 1, C) and a fall in heart rate. The average rise in mean blood pressure was 67 per cent. while the average fall in heart rate was 19 per cent. The average basal noradrenaline level was 0.09 ng. per ml. and that of adrenaline was 0.00 ng. per ml. The infusion, however, led to an increase in mean circulating plasma noradrenaline to 4.02 ng. per ml. and adrenaline rose to 0.13 ng. per ml. In the normal subjects there was also a rise in blood pressure with noradrenaline infusion and the extent of the rise in normals and tetraplegics is shown in figure 2.

DISCUSSION

The results obtained show the relationship in tetraplegic subjects between plasma catecholamines and changes in blood pressure. Previous reports have not given a consistent picture of catecholamine levels in tetraplegics at rest. Munro and Robinson (1958) and Guttmann *et al.* (1963) found that at rest the plasma catecholamines were low, but methods of estimation available at that time were rather inaccurate. Claus-Walker *et al.* (1971) examined catecholamines and their break-down products in the urine of tetraplegics and concluded that at rest they have nearly normal sympatho-adrenal function. Naftchi *et al.* (1972) also looked at urinary metabolites and argued that there is an increase in circulating noradrenaline in tetraplegics at rest. The present observations are on plasma, not on urine, and have been made with techniques where accuracy has been substantiated (Christensen, 1973). They support the view of Munro and Robinson (1958) and Guttmann *et al.* (1963) that levels of plasma catecholamines in tetraplegics at rest are low.

When the bladder of a tetraplegic subject is percussed, or his skeletal muscles are stimulated, plasma noradrenaline rises substantially so that it reaches the normal range. There is also a slight rise in adrenaline. Noradrenaline is the neurotransmitter at adrenergic sympathetic nerve endings and adrenaline is the principle secretion from the adrenal medulla. The preponderance of noradrenaline compared to adrenaline in the plasma of tetraplegics after bladder or muscle

stimulation suggests that the increase in plasma catecholamines is due to increased sympathetic nervous activity rather than adrenal secretion. This is consistent with the view put forward on clinical grounds by Head and Riddoch (1917), and supported by others (Guttmann & Whitteridge, 1947; Cunningham *et al.*, 1953; Kurnick, 1956; Roussan *et al.*, 1966; Corbett *et al.*, 1971a and b).

The question arises whether the increase in circulating noradrenaline can itself account for the increase in blood pressure, and the effect of a continuous infusion of noradrenaline bears on this. The pressor effect of infused noradrenaline and of bladder percussion were very similar, but the plasma levels of noradrenaline were very different; 4.02 ng. per ml. during the infusion and 0.19 ng. per ml. during bladder percussion. This suggests that the pressor effect is due to sympathetic activity and that the rise in plasma noradrenaline is secondary to this. It supports the view mentioned above.

The observations on noradrenaline infusion also provide evidence regarding supersensitivity of tetraplegics to this substance. Our controls were two normal subjects, while those taken from Goldenberg *et al.* (1948) were two normal male subjects aged 25 and 48 years. The evidence indicates that the pressor response to similar doses is greater in tetraplegic subjects than in normal subjects. This may be due to supersensitivity of blood vessels in the tetraplegics. It is, however, difficult to exclude the possibility that in the normal subjects homeostatic reflexes limited the pressor response, but that in the tetraplegics this was impossible as the lesion cuts off the higher circulatory control from the sympathetic outflow.

SUMMARY

1. Six patients with long-standing physiologically complete cervical spinal cord lesions and two normal subjects were examined.
2. In the tetraplegic subjects, arterial blood pressure, heart rate, plasma noradrenaline and adrenaline were measured at rest and during bladder percussion, during electrical stimulation of muscles and during infusion of noradrenaline.
3. In the normal subjects arterial blood pressure and heart rate were recorded before and during noradrenaline infusion.
4. Bladder percussion and muscle stimulation caused a rise in plasma noradrenaline from a subnormal level, together with a rise in blood pressure.
5. A similar rise in blood pressure due to noradrenaline infusion occurred at a very much greater level of plasma noradrenaline.
6. It is concluded that hypertension in tetraplegic subjects who have bladder percussion or muscle stimulation, is due to sympathetic overactivity rather than adrenal medullary secretion. Findings are consistent with, but not conclusive of, supersensitivity of the blood vessels of tetraplegic subjects to noradrenaline.

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