Plasma Catecholamines during Paroxysmal Neurogenic Hypertension in Quadriplegic Man


SUMMARY  Blood pressure, heart rate, and plasma catecholamine levels were measured in 16 quadriplegic subjects with physiologically complete cervical spinal cord transections above the level of the sympathetic outflow, and in 15 normal subjects (controls). In the quadriplegics the average resting blood pressure was 107/59 (mean, 75) mm Hg, heart rate was 65 beats/min, and plasma norepinephrine (NE) and epinephrine (E) levels were 0.05 and 0.005 ng/ml, respectively. In the controls average resting blood pressure was 117/79 (mean, 92) mm Hg, heart rate was 61 beats/min, and resting plasma NE and E levels were 0.20 and 0.06 ng/ml, respectively. Resting blood pressure and plasma NE and E levels were significantly lower in the quadriplegics (P < 0.01, < 0.001, < 0.001, and < 0.001, < 0.001, respectively) than in the controls. In the quadriplegics, neurogenic hypertension was induced by bladder and muscle stimulation. This resulted in a marked elevation of both botic and diastolic blood pressure (from an average of 109/60 (mean, 75) to 168/87 (mean, 114) mm Hg) as a result of uninhibited sympathetic nervous activity through the isolated spinal cord. Plasma NE consistently rose, from an average of 0.05 to 0.16 ng/ml (P < 0.001). There was a significant linear relationship between plasma NE and mean blood pressure (P < 0.001). The plasma NE concentration was 21 times higher than during muscle and bladder stimulation. It is possible that the lower resting arterial blood pressure and plasma NE and E levels in the quadriplegics in comparison to normal subjects may reflect diminished resting sympathetic nervous activity. The rise in blood pressure following increased sympathetic nervous activity was accompanied by an elevation in plasma NE. The hypertension was not secondary to the rise in plasma NE. Plasma NE in these subjects appears to be a reliable index of prevailing sympathetic nervous activity.

PLASMA NOREPIINEPHRINE (NE) is regarded as an index of sympathetic nervous activity and has been used, for instance, in the study of subjects with essential hypertension, diabetic neuropathy, myxedema, and thyrotoxicosis. To test further the reliability of this index we have studied plasma catecholamine levels in quadriplegic subjects with physiologically complete cervical spinal cord transections. These subjects do not have supraspinal control of their sympathetic outflow. They are prone to marked elevations of both systemic and diastolic blood pressure during cutaneous, visceral, and muscle stimulation which is a result of reflex sympathetic activity via the isolated spinal cord. We have measured plasma catecholamine levels and related them to arterial blood pressure before, during, and after hypertension resulting from an induced increase in sympathetic nervous activity.

Methods

We studied 16 quadriplegic subjects (13 male and three female) between 19 and 42 (mean, 27) years in age. All had physiologically complete cervical spinal cord transections between C4 and C7, with complete sensory and motor loss below the level of the transection. None was suffering from any systemic disease or complication. All subjects had normal values for serum creatinine, blood urea, and plasma electrolytes, and a normal intravenous pyelogram. All medications were withdrawn at least 48 hours before the investigation. None of the patients was bedridden and all were mobile in their wheelchairs. Informed consent was obtained from all, and the procedures were approved by the Ethics of Research Committee of Stoke Mandeville Hospital. Some subjects volunteered for the study on more than one occasion. Fifteen healthy normal subjects (13 male and two female) between 21 and 38 (mean, 27) years in age were studied as controls. None was on drug therapy or had any systemic disease.

Subjects and controls were studied in the supine position. The quadriplegics were brought directly from the ward on their beds and transferred to a bed in the laboratory, with care to prevent undue movement or spasms. A polytetrafluoroethylene (Teflon) catheter was introduced percutaneously into either the dorsalis pedis, femoral, or radial artery. The catheter was connected via saline-filled manometer tubing to an electromagnetic, which was placed on a level with the 4th intercostal space, just anterior to the midaxillary line (the phlebostatic axis). Between the catheter and the electromagnetic was a device which provided both continuous perfusion with sterile heparinized saline and also series mechanical damping of the arterial pressure system by an adjustable stop. The blood pressure signal triggered a beat-to-beat heart rate meter. Blood pressure and heart rate signals were led into a four-channel rectilinear pen recorder. The electrocardiograph (ECG) was displayed continuously on an oscilloscope, and recordings were made when required. For the quadriplegics, blood samples for the measurement of plasma NE and epinephrine (E) were taken after 30 minutes of rest. Blood was withdrawn via a three-way
connecter attached to the arterial catheter, care being taken that the blood sample did not contain perfusate. In 10 quadriplegics hypertension was induced by cutaneous and visceral stimulation ("bladder stimulation") (Fig. 1) which was effected by suprapubic percussion of the anterior abdominal wall for 2-3 minutes. Blood samples were taken at the end of this period and, in some cases, at subsequent intervals of up to 30 minutes. In another six quadriplegics, hypertension was induced by electrical muscle stimulation, care being taken that the electrode was not placed over the same area of skin for more than a few seconds to avoid burns. Blood samples again were taken at the end of this period and, in some cases, at subsequent intervals following this. In eight quadriplegics, l-norpinephrine (Levophed, Winthrop Laboratories), was infused intravenously at rates between 0.07 and 0.15 μg/kg per min, using a continuous infusion pump. Samples for measurement of NE and E were taken before and during the infusion.

Blood for measurement of plasma NE and E was immediately transferred to ice-cooled plastic tubes containing ethylenediaminetetraacetic acid (EDTA) and ascorbic acid (2 mg of each per ml of whole blood), placed in ice, and centrifuged at 3,000 rpm at 4°C for 10 minutes. Plasma was pipetted into ice-cooled plastic storage tubes and stored at −20°C until analyzed. Plasma NE and E were assayed using a modification of the double-isotope derivative technique of Engelman and Portnoy.10,11

For the controls, blood pressure was measured by sphygmomanometer, heart rate manually from the radial pulse, and blood for measurement of plasma NE and E was taken via an indwelling catheter in a vein in the cubital fossa. The blood was processed and assayed for NE and E using methods described above. Previous studies have shown that plasma NE and E concentrations are the same in arterial and in venous blood.10,11 To confirm this finding venous blood was collected from seven quadriplegics on 10 occasions under conditions identical to those used for the controls, and processed and assayed for NE and E as described above.

Mean blood pressure (MBP) was calculated from systolic and diastolic blood pressure using the formula: MBP = 1/3 pulse pressure + diastolic blood pressure. The data were statistically analyzed using Student's t-tests and paired t-tests. Regression analysis was performed with the blood pressure and plasma NE data from the quadriplegics and tests of significance applied to the correlation coefficients.

**Results**

In the quadriplegics average resting blood pressure from the three studies combined was 107/59 (mean, 75) mm Hg, the resting heart rate was 65 beats/min, and resting plasma NE and E levels were 0.05 and 0.005 ng/ml, respectively (Tables 1 and 2, Fig. 2). In the quadriplegics plasma NE and E levels in venous blood were 0.06 and 0.007 ng/ml, respectively, similar to levels in arterial blood. In the controls, the average resting blood pressure was 117/79 (mean, 92) mm Hg, the resting heart rate was 61 beats/min, and resting plasma NE and E levels were 0.20 and 0.005 ng/ml, respectively. In the quadriplegics, the systolic, diastolic, and mean blood pressure, and plasma NE and E levels were significantly lower than in the controls (P < 0.01, < 0.001, < 0.001, and < 0.001, < 0.001, respectively).

In the quadriplegics, the induction of hypertension by bladder stimulation resulted in an increase in average blood pressure from 109/59 (mean, 75) mm Hg to 184/92 (mean, 123) mm Hg. The increase being statistically significant (P < 0.01, < 0.01, < 0.001, respectively) (Table 1). There was also a significant decrease in heart rate, from an average of 68 to 53 beats/min (P < 0.001). The increase in plasma NE

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**Figure 1** Effect of bladder stimulation (B.S.) on the blood pressure (BP) and heart rate (HR) of a quadriplegic subject.

**Table 1** Blood Pressure (BP), Mean Blood Pressure (MBP), Heart Rate (HR), and Plasma Norepinephrine (NE) and Epinephrine (E) Levels in Quadriplegic Subjects at Rest and during Bladder and Muscle Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stimulation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bladder stimulation (n = 10)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>109 ± 2.6/59 ± 1.9</td>
<td>184 ± 9.6/92 ± 4.7</td>
<td>&lt;0.001/0.001</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>75 ± 2.3</td>
<td>123 ± 6.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>68 ± 3.6</td>
<td>53 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NE (ng/ml)</td>
<td>0.05 ± 0.012</td>
<td>0.18 ± 0.024</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>E (ng/ml)</td>
<td>0.01 ± 0.003</td>
<td>0.03 ± 0.011</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td><strong>Muscle stimulation (n = 6)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BP (mm Hg)</td>
<td>108 ± 5.2/61 ± 1.4</td>
<td>151 ± 9.9/82 ± 4.5</td>
<td>&lt;0.001/0.005</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>77 ± 2.5</td>
<td>105 ± 6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>58 ± 2.7</td>
<td>56 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>NE (ng/ml)</td>
<td>0.04 ± 0.012</td>
<td>0.14 ± 0.018</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>E (ng/ml)</td>
<td>0.002 ± 0.002</td>
<td>0.02 ± 0.003</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM; n = number of subjects; NS = not significant.
had fallen appreciably 3-5 minutes after the cessation of stimulation, when the blood pressure also had begun to fall toward previous resting levels. Mean blood pressure and plasma NE levels and the level of plasma NE (Fig. 3) but not E levels. The changes. Average blood pressure rose from 108/61 (mean, 77) mm Hg to 151/82 (mean, 105) mm Hg, respectively (P < 0.001, < 0.005, < 0.001, respectively). The fall in average heart rate from 58 to 56 beats/min was not significant. The average plasma NE level rose from 0.04 to 0.14 ng/ml and the average plasma E level from 0.002 to 0.02 ng/ml (P < 0.005, < 0.005, respectively).

For six quadriplegics, measurements of arterial blood pressure, heart rate, and plasma NE and E were made before, during, and at intervals after bladder and muscle stimulation. In all subjects there was an increase in blood pressure and plasma NE (Fig. 3) but not E levels. The greatest increase in plasma NE levels occurred during the maximum blood pressure rise, and the level of plasma NE had fallen appreciably 3-5 minutes after the cessation of stimulation, when the blood pressure also had begun to fall toward previous resting levels. Mean blood pressure and plasma NE levels were linearly correlated (Fig. 4), the relationship being significant (r = 0.7326, P < 0.001, y = 63.61 + 250.11x).

Intravenous infusion of l-norepinephrine (0.07-0.15 µg/kg per min) resulted in a marked elevation in average blood pressure from 105/58 (mean, 74) mm Hg to 183/93 (mean, 123) mm Hg (Table 2). This rise was comparable to the hypertension caused by bladder and muscle stimulation (Table 1). Heart rate fell from an average of 68 to 52 beats/min. Mean plasma NE and E levels rose from 0.05 and 0.004 ng/ml to 3.28 and 0.08 ng/ml, respectively. The plasma NE levels during infusion were 8-37 times higher than the mean plasma NE levels obtained during bladder and muscle stimulation.

**Discussion**

Resting levels of plasma NE and E were significantly lower in the quadriplegics than in the controls, a finding we have previously reported.14 Earlier workers also reported levels which were subnormal, though not as low as those reported above.14 It may be that their values differ because of the relative insensitivity of the methods available at that time. Furthermore, their measurements were made with the subjects sitting, and the precise method of blood collection is not described. This may be relevant, because cutaneous atonia and account for the lower resting levels of both plasma NE and E in our quadriplegics are probably the result of a reduction in sympathetic nervous activity due to the loss of impulses from supraspinal centers. This may result in vasomotor atonia and account for the lower resting blood pressure in the quadriplegics. There probably is residual reflex sympathetic activity through the isolated spinal cord, due to minimal superficial and deep stimuli, and this may account for the small amounts of plasma NE present at rest.

Previous discussions of catecholamines during neurogenic hypertension in quadriplegics have been based on changes in urinary but not plasma catecholamine levels. It was origi-
nally reported that there was no change in the urinary excretion of catecholamines during hypertension induced by retrograde bladder filling. Subsequent investigators reported increased urinary excretion of catecholamines and their metabolites during the hypertension accompanying bladder distention and activity. The sensitivity and specificity of some of the methods used are open to criticism, and scant mention is made of the drugs these subjects were taking which may have interfered with the analysis. Furthermore, urinary excretion of these substances is dependent on urine flow, urine pH, and renal function, which are not discussed. The increased sympathetic activity and hypertension that accompany bladder activity might affect renal blood flow and urinary flow, and quadriplegics are prone to urinary tract infections, which can cause changes in urinary pH and result in renal damage. The conclusions from previous reports based on measurements of catecholamines and their metabolites in urine, therefore are subject to limitations. Further, it is not possible to relate excretion of catecholamine metabolites over a prolonged period of time, to arterial blood pressure at a particular time. Values for plasma catecholamines measured by the methods we have used are not subject to these criticisms.

In our quadriplegic subjects, hypertension induced by bladder or muscle stimulation resulted in a significant rise in plasma NE. Mean blood pressure and plasma NE were directly correlated (Fig. 4). Plasma NE peaked with the peak blood pressure, and fell toward resting levels along with the blood pressure (Fig. 3). This is in contrast to results in similar subjects of studies on plasma dopamine β-hydroxylase (D-β-H). The enzyme released proportionally with NE from sympathetic nerve endings. When sympathetic nervous activity is induced by bladder stimu-
lation, plasma D-β-H levels rise, but are highest a few minutes after the cessation of stimulation and peak blood pressure, by which time the blood pressure has fallen appreciably. D-β-H is a larger molecule than NE and its entry into the circulation may be retarded by capillary barriers. Therefore, D-β-H has been demonstrated in human lymph, and experiments on the dog, during sympathetic activation, suggest that a major portion of D-β-H released from adrenergic nerve terminals is transported in lymph before it enters circulating blood. This may account for the slower passage of D-β-H from the neuroeffector junction into the circulation.

The possibility was considered that the hypertension was due to circulating NE rather than to reflex sympathetic activity that resulted in a secondary increase in plasma NE. The levels of plasma NE during neurogenic hypertension, however, did not exceed the resting levels in normal man. Furthermore, infusion of NE into quadriplegics produced comparable rises in blood pressure but the plasma NE levels required were approximately 8–37 times the levels observed during bladder and muscle stimulation. Circulating NE, therefore, does not appear to be responsible for hypertension due to bladder and muscle stimulation. In another study which used graded intravenous infusions of l-norepinephrine into similar subjects, an enhanced pressor response to NE, compared to normal subjects, has been demonstrated. It is thought that this may be due to an increased adrenergic receptor response or, more likely, to the lack of blood pressure-restraining reflexes, notably those baroreceptor reflexes with sympathetic effenter pathways. The lesion in our quadriplegics resulted in a severance of descending supraspinal sympathetic pathways. Reflex sympathetic discharge through the isolated spinal cord, uninfluenced by inhibitory pathways, is therefore a likely cause of the severe hypertension which results from bladder and muscle stimulation.

Our evidence indicates that quadriplegics have a lower resting arterial blood pressure and plasma NE and E levels than normal subjects. In the quadriplegics there is a significant rise in plasma NE levels which accompanies induced neurogenic hypertension. Blood pressure is linearly related to plasma NE levels. Plasma NE in such subjects appears to be a reliable index of sympathetic nervous activity.

Acknowledgments

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