Abolition, by dopamine blockade, of the natriuretic response produced by lower-body positive pressure

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Summary

1. In a preliminary study, a positive pressure of 25 mmHg applied to the lower body raised right atrial pressure by a mean of 7 mmHg.

2. Sustained application of lower-body positive pressure (LBPP) in six normal adult males increased sodium excretion (\(\text{[Na]}\)\(V\)) from a control level of \(126.5 \pm 10\) pmol/min to \(213 \pm 21\) pmol/min \((P = 0.003)\) and fractional sodium excretion \(\left(\text{EF}_{\text{Na}}\right)\) from \(0.7 \pm 0.1\) to \(1.2 \pm 0.1\) \((P = 0.001)\).

3. Urine flow (UF) increased from \(0.85 \pm 0.07\) ml/min to \(4.1 \pm 0.8\) ml/min \((P = 0.002)\), osmolar clearance \(\left(C_{\text{osm}}\right)\) from \(2.6 \pm 0.13\) ml/min to \(4.2 \pm 0.4\) ml/min \((P = 0.003)\) and free water clearance \(\left(C_{\text{H2O}}\right)\) from \(-1.75 \pm 0.1\) ml/min to \(-0.1 \pm 0.01\) ml/min \((P = 0.001)\). Creatinine clearance \(\left(C_{\text{cr}}\right)\) showed no significant change.

4. After dopamine blockade with domperidone, LBPP did not cause a rise in \([\text{Na}]\)\(V\) or \(\text{EF}_{\text{Na}}\). However, urine flow, \(C_{\text{osm}}\), and \(C_{\text{H2O}}\) remained significantly above control values, implying persistent suppression of antidiuretic hormone.

5. Dopamine blockade without positive pressure did not affect basal sodium excretion.

Key words: dopamine blockade, lower-body positive pressure, natriuresis, sodium.

Abbreviations: \(\text{EF}_{\text{Na}}\), fractional sodium excretion; LBPP, lower-body positive pressure.

Introduction

In several studies Epstein [1, 2] and his colleagues have shown that prolonged immersion to the neck in a temperature-controlled water bath causes marked diuresis and natriuresis. Arborelius et al. [3] have demonstrated that such water immersion has marked haemodynamic effects in substantially raising intracardiac filling pressures, cardiac output and redistributing approximately 750 ml of blood into the central circulation.

Other workers have demonstrated that direct stimulation of left atrial receptors [4, 5], or increasing intracardiac filling pressures [6, 7] is associated with marked elevation of sodium and water excretion. More recently, Kass [8] and his colleagues showed that sustained application of lower-body positive pressure (LBPP) in baboons also results in a natriuresis, but this response has a circadian rhythm. The precise mechanism responsible for these changes is uncertain, although it has been suggested that changes in endogenous dopamine production may play a role. Alexander et al. [9] have shown a rise in urinary dopamine excretion in volume-expanded normal subjects. Ball & Lee [10] showed that the administration of carbidopa reduced both urinary dopamine and sodium excretion in man, and Brown & Dollery [11] found that dopamine blockade in DOCA-treated rats substantially attenuated the natriuretic response.

The preliminary study was carried out to show that intracardiac filling pressure could be elevated systematically by applying lower-body positive pressure (LBPP) in a stepwise fashion.

The main study, therefore, was designed to determine whether dopamine blockade could...
attenuate the natriuretic response associated with an increase in intracardiac filling pressure. It was also designed to examine whether changes in urinary dopamine excretion were related to the natriuretic response.

In addition, a separate control study was carried out to measure the effect of dopamine blockade on basal sodium excretion.

**Materials and methods**

**Preliminary study**

A thin Teflon catheter was passed percutaneously to the superior caval right atrial junction in three normal male subjects. Right atrial pressure was recorded by using a Statham P23Db pressure transducer, with mid-thorax taken as zero reference point. Before the introduction of the catheter, the subject was placed in a specially designed plastic bag. The bag allowed the subject to sit in the upright position with the legs dependent. The bag was sealed around the subject just below the costal margin. The bag was then inflated to pressures of 5, 10, 15 and 25 mmHg, a commercial vacuum cleaner reversed to act as a pump being used. Each inflation pressure was maintained for 5–10 min, and right atrial pressure measured at the end of each period.

**Main study**

Six normal adult male volunteers (aged 18–40 years) were studied. They were put on a diet containing 150 mmol of sodium/24 h. During the subsequent 2 days they continued with normal activities. On the third day of the diet the subjects came to the laboratory at 08.30 hours. For the next 30–40 min they sat comfortably in a chair. They then emptied their bladders, the urine being discarded. The study was then commenced at approximately 09.00 hours. The subjects remained at rest for the next 2 h. Urine was then collected at the end of this period and a blood sample taken. Further urine collections were made at the end of 90 min.

Urine flow rates were calculated and the urine was analysed for sodium concentration with a Flame 4 autoanalyser. Plasma sodium concentration was measured with the same technique. Urine and plasma creatinine were measured on the same machine. Plasma and urine osmolality were obtained with an Advanced Instruments Incorporated Osmometer. From these results the following calculations were made: urine flow in ml/min; sodium excretion ([Na+]V) in μmol/min; creatinine clearance (Ccr) in ml/min; osmolar clearance (Cospm) in ml/min; free water clearance (CfH2O) in ml/min; fractional sodium excretion (EFNa).

At a separate time, six subjects were placed on 150 mmol/day sodium diet. On the fourth day the subjects came to the laboratory and rested for 30 min and then emptied their bladders. They were then told that they were to receive an injection of either glucose solution or 40 mg of domperidone. In fact the glucose was always given first. Urine was collected after a 60–90 min period. A bolus of domperidone (40 mg) was then given and a blood sample taken. Further urine collections were made at the end of 90 min.

Freeze-drying of portions (100 μl) of the acetic acid eluate was followed by incubation at 65 °C for 40 min with 20 μl of acetonitrile and 100 μl of pentafluoropropionic anhydride. Excess reagent was evaporated in a stream of nitrogen and the
Natriuresis and dopamine blockade

TABLE 1. Effects on renal function of lower-body positive pressure alone and of LBPP plus dopamine blockade

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<tr>
<th></th>
<th>Control</th>
<th>Inflation</th>
<th>Blockade</th>
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<tbody>
<tr>
<td>Sodium excretion (nmol/min)</td>
<td>127 ± 10</td>
<td>213 ± 21***</td>
<td>131 ± 14†††</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>0.85 ± 0.07</td>
<td>4.1 ± 0.8***</td>
<td>2.6 ± 0.6***</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>144 ± 6</td>
<td>127 ± 7</td>
<td>135 ± 6</td>
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<tr>
<td>Osmolar clearance (ml/min)</td>
<td>2.6 ± 0.1</td>
<td>4.2 ± 0.4***</td>
<td>2.9 ± 0.2†††</td>
</tr>
<tr>
<td>Fractional sodium excretion</td>
<td>0.7 ± 0.1</td>
<td>1.2 ± 0.1***</td>
<td>0.7 ± 0.1†††</td>
</tr>
<tr>
<td>Free water clearance (ml/min)</td>
<td>-1.75 ± 0.1</td>
<td>-0.1 ± 0.01***</td>
<td>-0.4 ± 0.02***</td>
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<th>P values</th>
<th>0.001</th>
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<td>Control/inflation</td>
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<td>Control/blockade</td>
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<tr>
<td>Inflation/blockade</td>
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Pentafluoropropionyl derivatives were dissolved in 200 μl of heptane. Portions (0.3 μl) were injected on to a column packed with 10% SE 54 (J.J. Chromatography) on Chromosorb W (HP) 100/120 mesh in a Hewlett Packard 5700 gas chromatograph run isothermally at 200 °C in a 25 ml/min stream of argon/methane carrier gas with 63Ni electron capture detector. Retention times for dopamine and isoprenaline were 6.8 and 7.4 min respectively. Dopamine excretion rate was expressed in nmol/min.

Statistical analysis was carried out by Student’s paired t test.

Results

Fig. 1 shows the change in right atrial pressure as the inflation pressure in the bag was increased. There was a systematic rise in the right atrial pressure as the bag pressure increased so that at a bag pressure of 25 mmHg the mean rise in the atrial pressure was 7.7 mmHg.

Table 1 shows the changes in urine flow, [Na]V, Efr, Ccr, Cosm, and CH2O during the course of the experiment.

Compared with the control period, the application of LBPP almost doubled [Na]V (P = 0.003); urine flow showed an almost fivefold increase (P = 0.003). Both Cosm and Efr almost doubled (P = 0.003, P = 0.001). CH2O also increased significantly (P = 0.001) and Ccr showed no significant change.

The administration of domperidone abolished the increase in [Na]V due to LBPP. [Na]V was significantly lower than during LBPP alone (P = 0.003); it was now not significantly different from the control value. Urine flow showed only a small insignificant decrease, remaining significantly greater than the control value (P = 0.003). Cosm fell significantly (P = 0.05), but was still significantly greater than control (P = 0.05). Similarly, CH2O showed no significant change, remaining significantly greater than control value (P = 0.001).

There was no significant difference in mean urinary dopamine excretion during the course of the experiment: control 1.65 ± SEM 0.38; LBPP alone 1.76 ± 0.12; LBPP + domperidone 1.34 ± 0.26 nmol/min.

Table 2 shows the results of domperidone administration on basal sodium excretion: there were no significant changes in any of the variables.

Discussion

The data in our preliminary study confirm that LBPP is a satisfactory method of increasing

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<tr>
<td>ΔRAP (mmHg)</td>
<td>2.9</td>
<td>6.0</td>
<td>8.0</td>
<td>9.0</td>
<td>7.5</td>
<td>6.0</td>
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FIG. 1. Changes in right atrial pressure (RAP) as a result of pressure applied by the bag. Mean values ± SEM are shown.
intracardiac pressure. The mean rise of over 7 mmHg in the central venous pressure is similar to that obtained by Arborelius et al. [3] in studies made on normal subjects immersed in a water bath, when they also demonstrated marked increases in pulmonary capillary wedge pressure and cardiac output.

The changes in sodium and urine excretion found in our study are very similar to those demonstrated by Epstein and his colleagues [1], also using water immersion. They showed a progressive rise in sodium excretion over a 5 h period, a much longer time than in the present study. They also showed that the increase in sodium excretion resulted from changes in tubular reabsorption, a result confirmed in the present study, where no change in creatinine clearance was noted. Epstein also demonstrated that the increase in urine flow and \( C_{H_2O} \) were due to suppression of production of antidiuretic hormone and that diuresis could be entirely abolished by the administration of vasopressin [14]. However, this did not affect natriuresis.

Epstein has discussed the mechanisms responsible for the natriuresis. These include changes in renin–angiotensin activity, in aldosterone production, in Starling forces, redistribution of renal blood flow or alteration of sympathetic tone to the kidney. He concluded that it was unlikely that any of these mechanisms were responsible [14]. He also suggested that a humoral factor may be responsible and he demonstrated that an extract of the urine of subjects undergoing water immersion produced a natriuresis when injected into rats [15]. This is in agreement with the results obtained by Brown et al. [16], who demonstrated similar results with volume-expanded animals. It has been suggested that the release of a sodium, potassium-dependent ATPase inhibitor by the hypothalamus may be responsible for this effect [17].

Other workers have suggested that endogenous renal dopamine may play a role in the control of sodium excretion. Alexander et al. [9] demonstrated that normal subjects volume-expanded with sodium chloride solution (150 mmol/l) showed a tripling of their sodium excretion and a significant increase in urinary dopamine excretion. They also showed a significant relationship between sodium and dopamine excretion in subjects on low and high sodium diets. Faucheux et al. [18], however, showed convincingly that volume-expansion with salt-free albumin did not increase urinary sodium or dopamine excretion. Faucheux also showed that the increase in dopamine excretion associated with saline volume-expansion lagged behind the increase in sodium excretion, and he suggested that the increased dopamine excretion may be purely a secondary effect. Our inability to detect any change in dopamine excretion during LBPP is therefore compatible with these results. Furthermore, re-examination of Alexander's data shows the same phenomenon in that sodium excretion showed a marked increase during the first 90 min of the experiment with no change in dopamine excretion. Only much later did dopamine excretion increase with a further increase in sodium excretion. Ball et al. [19] implied that the presence of the chloride ion was important in obtaining an increase in urinary dopamine after volume-loading.

Imondi et al. [20] and Brown & Dollery [11] have shown that dopamine blockade with sulpiride or domperidone considerably reduces the response to volume-loading in rats in terms of both sodium and dopamine excretion. Furthermore, Ball & Lee [10] found that the administration of the decarboxylase inhibitor, carbidopa, caused a significant decrease in both urinary dopamine and sodium excretion in normal subjects.

In the present study the administration of the dopamine-blocking agent, domperidone, totally abolished the natriuretic response to LBPP. On the other hand, no effect was seen on urine flow and \( C_{H_2O} \). This implies that dopamine blockade did not interfere with the suppression of antidiuretic hormone. We were unable to find any changes in urinary dopamine excretion over the short time course of our study.

The additional study demonstrates that domperidone has no significant effect on basal sodium excretion and strongly suggests that dopamine blockade during LBPP abolishes the natriuretic response produced by this manoeuvre.

Domperidone is a peripheral dopamine receptor blocking agent which does not cross the blood–brain barrier [21]. It has been reported by J. M. Van Neuten, L. Helsen & C. Ennis

<table>
<thead>
<tr>
<th>TABLE 2. Effects of dopamine blockade on basal sodium excretion Mean values ± SEM are shown.</th>
<th>Placebo</th>
<th>Blockade</th>
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<tbody>
<tr>
<td>Sodium excretion (( \mu \text{mol/min} ))</td>
<td>171 ± 35</td>
<td>156 ± 32</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>3.98 ± 0.7</td>
<td>4.06 ± 1.1</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>111 ± 11</td>
<td>112 ± 14</td>
</tr>
<tr>
<td>Osmolar clearance (ml/min)</td>
<td>2.99 ± 0.4</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>Fractional sodium excretion</td>
<td>1.09 ± 0.18</td>
<td>0.99 ± 0.15</td>
</tr>
<tr>
<td>Free water clearance (ml/min)</td>
<td>0.99 ± 0.68</td>
<td>1.26 ± 0.96</td>
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(Seventh International Congress of Pharmacology, Paris) to block the effects of dopamine on the gut. However, L. M. Goldberg—personal communication) has recently demonstrated that domperidone does not block the renovascular response to LBPP remains unclear, but several possibilities exist. Firstly, it may be blocking a direct effect of endogenous renal dopamine on tubular reabsorption of sodium, although there is no evidence to confirm this. Secondly, domperidone may inhibit the release of a natriuretic factor in which dopamine may be one element of a cascade. Thirdly, stimulation of aldosterone production could lead to a reduction in sodium excretion. Although the dopamine blocking agent metoclopramide has been shown to increase aldosterone production [22], domperidone does not have this effect [23]. It is unlikely, therefore, that changes in aldosterone can account for the anti-natriuretic effect of domperidone.

A fourth possibility is the increase in plasma prolactin that dopamine-blocking agents have been shown to produce. Domperidone, metoclopramide and sulpiride all increase plasma prolactin concentration [22, 24–26]. Furthermore, the administration of ovine prolactin to normal subjects has been shown to cause a marked sodium retention for up to 6 h [27]. In addition, Lucci et al. [28] found that the natriuretic response to saline expansion was significantly blunted by the prior administration of ovine prolactin. However, prolactin did not blunt the response to volume-expansion with blood. In contrast, Baumann et al. [29] found that acute elevation of endogenous prolactin did not produce any reduction in sodium excretion.

On the other hand, Karmali et al. [30] found that prolactin production showed a threefold reduction when normal subjects were placed in a hyperbaric chamber. This is a condition similar to that produced by LBPP in the present experiment.

The results of our study on the effects of dopamine blockade on basal sodium excretion would seem to exclude any major role for prolactin in its short-term regulation. As domperidone increases prolactin production, a decrease in sodium excretion might have been expected after its administration. This was not found. We are therefore unable to define by what mechanism dopamine inhibits the response to LBPP.

**References**


[3] Arro realised, M., Ball et al. (1973) Endogenous renal dopamine on the gut. However, L. M. Goldberg—personal communication) has recently demonstrated that domperidone does not block the renovascular response to LBPP remains unclear, but several possibilities exist. Firstly, it may be blocking a direct effect of endogenous renal dopamine on tubular reabsorption of sodium, although there is no evidence to confirm this. Secondly, domperidone may inhibit the release of a natriuretic factor in which dopamine may be one element of a cascade. Thirdly, stimulation of aldosterone production could lead to a reduction in sodium excretion. Although the dopamine blocking agent metoclopramide has been shown to increase aldosterone production [22], domperidone does not have this effect [23]. It is unlikely, therefore, that changes in aldosterone can account for the anti-natriuretic effect of domperidone.

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