The Effect of Posture on Hypertension Induced by Sympathomimetic Amines in Man

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After atropine the hypertension induced by Arterenol in man is abolished by tilting to the vertical position. This does not occur with equipressor doses of Arterenol or with atropine alone. Arterenol and atropine in combination could not be shown to have a blocking action at sympathetic ganglia in animal experiments, nor was there blockade of the carotid sinus reflex pathways. The failure to maintain Arterenol-induced hypertension after atropine was thus unexplained. Further experiments on the clinical implications of this phenomenon were performed.

In previous studies on the effect of atropine in increasing the pressor response to Arterenol (norepinephrine) in man, we found in one subject that the headache associated with the hypertension disappeared on rising from the supine to the erect position. On determining the blood pressure after the subject stood up it was found to have fallen from 190/110 mm. Hg to 70/50. On reclining the previous high level of pressure was found to have returned.

The phenomena associated with the pressor effect of Arterenol are of interest because of the presence of this amine in the adrenal medulla and in epinephrine preparations of natural origin. Arterenol has also been considered by Goldenberg and co-workers as a possible mediator in essential hypertension.

The present studies were performed to find out how consistently the postural depressor response occurred, and to study its mechanism.

Blood Pressure Response to Arterenol and Atropine and Tilting

Blood pressure was measured by the usual clinical auscultatory method. The heart rate was counted for one-half minute by precordial auscultation, or, if satisfactory, by palpation of the radial pulse.

Before the tilt the blood pressure and heart rate were determined at one minute intervals. When these were stable the table was tilted rapidly to the nearly vertical position. Readings were made at one-half or one minute intervals, beginning immediately on completing the tilt. After 5 to 10 minutes the table was returned to the horizontal and readings continued at one or two minute intervals for 10 minutes.

1. Tilting from the horizontal to the nearly vertical position (about 80°) without drugs.

This was performed on nine normal young men to ascertain that all subjects had normal postural compensatory reflexes, namely, a rise in diastolic pressure of 10 to 20 mm. Hg and either a slight rise or fall in systolic pressure with an increase in heart rate of up to 20 beats per minute.

2. Similar tilting after atropine in doses of 1.0 to 4.0 mg. (five subjects); after 0.1 to 0.8 mg. of l-Arterenol base* (five subjects); and after various doses of both drugs given together (16 experiments on six subjects).

The drugs were injected subcutaneously, the Arterenol being given about one hour after atropine. This order was necessary because the peak pressor effect of Arterenol by this route

lasted only about 20 minutes. The various experiments were performed on separate days to avoid overlapping of drug effects. The results were as follows:

![Graph showing pressor response to various doses of Arterenol with and without atropine]

**Fig. 1.** Pressor response to various doses of Arterenol with and without atropine.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Atropine mg.</th>
<th>L-Arterenol base mg.</th>
<th>Pretilt Rise in Blood Pressure (Peak, mm. Hg)</th>
<th>Vertical Position Maximum Drop in B.P. from Pretilt Peak</th>
<th>Maximum change in heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Syst.</td>
<td>Diast.</td>
<td>Syst.</td>
</tr>
<tr>
<td>R. C.</td>
<td>1.0</td>
<td>0.1</td>
<td>10</td>
<td>0</td>
<td>+8</td>
</tr>
<tr>
<td>L. B.</td>
<td>1.0</td>
<td>0.2</td>
<td>18</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>L. B.</td>
<td>1.0</td>
<td>0.2</td>
<td>18</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>R. C.</td>
<td>1.0</td>
<td>0.2</td>
<td>34</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>L. B.</td>
<td>1.0</td>
<td>0.3</td>
<td>48</td>
<td>32</td>
<td>60</td>
</tr>
<tr>
<td>M. G.</td>
<td>2.0</td>
<td>0.1</td>
<td>42</td>
<td>44</td>
<td>54</td>
</tr>
<tr>
<td>A. L.</td>
<td>2.0</td>
<td>0.3</td>
<td>68</td>
<td>36</td>
<td>120</td>
</tr>
<tr>
<td>A. L.*</td>
<td>2.0</td>
<td>0.4</td>
<td>74</td>
<td>32</td>
<td>45</td>
</tr>
<tr>
<td>D. F.*</td>
<td>4.0</td>
<td>0.4</td>
<td>52</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>R. G.*</td>
<td>6.0</td>
<td>0.04</td>
<td>18</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>A. L.</td>
<td>0.5 (I.V.)</td>
<td>0.8</td>
<td>120</td>
<td>50</td>
<td>150</td>
</tr>
</tbody>
</table>

* In these experiments a tilt-table was not available. The subjects stood at the bedside.

**Atropine.** In no case did hypotension occur with tilting. There was the same blood pressure response as in the control experiments, with a greater increase in heart rate.

**Arterenol.** The maximum pressor responses to Arterenol injected subcutaneously are shown in figure 1. Repeated doses of the same amount on different days gave closely similar responses. On tilting there was little change in blood pressure. There was no decrease in intensity of the headache in the upright position.

**Arterenol after atropine.** After atropinization the administration of Arterenol resulted in a hypertension of greater magnitude than that which was produced by equal doses of Arterenol alone (fig. 1). On tilting, the hypertension would give way to hypotension. Measuring from the peak pretilt pressure levels, there was a fall in systolic pressure of 20 to 150 mm. Hg and a fall in diastolic pressure of 7 to 70 mm. Hg in 10 experiments (table 1). In one experiment (experiment 1), after atropinization a small dose of Arterenol was used and no diastolic pressor response was obtained. In this experiment the subject showed a normal response to tilting, whereas in another experiment (experiment 4) with a larger amount of Arterenol (enough to produce hypertension) the same subject showed a hypotensive response to tilting. Throughout the series there was a clear correlation between the magnitude of the pressor response and the magnitude of the drop in pressure on tilting to the vertical position.

In each of the experiments in this group the headache was absent in the vertical position. The other symptoms induced by Arterenol,
such as palpitation and dyspnea, were diminished, and the subject felt much better when upright. Promptly on return to the horizontal position the hypertension returned to the pretilt level and the symptoms also returned.

In two experiments the drop in pressure with upright position was prevented by the application of blood pressure cuffs to both thighs, and inflation to 250 mm. Hg immediately before tilting. When the cuffs were deflated while the subject was still upright there was a sudden drop to low levels. This experiment shows that intravascular pooling in the legs accounts for at least part of the drop in blood pressure.

**Discussion and Studies on Animals**

There are two general kinds of mechanisms which can be suggested to explain the failure to maintain blood pressure, after Arterenol and atropine, on tilting to the upright position.

First, failure of compensatory arteriolar concretion is to be considered. This could be due to a defect in either the afferent or efferent limbs of the postural vasoconstrictor reflexes.

To investigate the possibility that Arterenol and atropine might block carotid sinus reflexes the following experiments were performed: Three dogs were lightly anesthetized with sodium pentobarbital and one carotid artery was cannulated for the recording of blood pressure. Small pressor doses (10 gamma of base) of l-Arterenol were given intravenously. At the moment of the peak of the pressor response, the carotid which had not been cannulated was compressed low in the neck. A second peak occurred; the magnitude of the pressor response to carotid clamping was greater than that due to the dose of Arterenol used. These experiments were repeated several times after the intravenous administration of 1.0 mg. of atropine. Atropinization regularly caused slight augmentation of the pressor response to Arterenol. The response to carotid clamping after both drugs was irregularly, and at most only slightly, decreased.

The postural constrictor reflexes could be blocked at two possible sites in the efferent limb, namely, at sympathetic ganglions or at effector cells.

A study of the combined action of Arterenol and atropine on the superior cervical sympathetic ganglion of the cat was next undertaken.

In five cats under light anesthesia with sodium pentobarbital, an electrode was placed on the cervical sympathetic trunk. Movement of the nictitating membrane was recorded by means of a pulley and lever system, and blood pressure by means of a mercury manometer. A constant current was applied to the electrode with the lowest intensity which would maintain retraction of the membrane. Moderate pressor doses of Arterenol did not affect the retraction. After atropinization there was no consistent change with repeated doses of Arterenol.

There would remain a possibility that the adrenotropic receptors under the influence of Arterenol would be blocked to the neurohumoral mediators liberated by the reflex constrictor impulses. This is excluded by the regular occurrence of a pressor response to carotid sinus stimulation in the dog after Arterenol and atropine as described above.

Another possibility is that of postarteriolar vascular dilatation, as has been described for the syncope-producing effect of nitrites.

However, with nitrites the blood pressure is maintained in the vertical position with severe symptoms until collapse finally occurs. In our experiments the subjects felt better in the upright position, with relief of the symptoms due to the sympathetic drugs and with no tendency to collapse.

We therefore regard the postural drop in pressure after Arterenol and atropine as unexplained.

**Clinical Implications; Further Experiments**

Goldenberg has suggested that Arterenol could be the humoral agent which mediates essential hypertension in man. On the basis of the foregoing observations, if circulating Arterenol were present in pressor amount, a postural drop in pressure could be expected after the administration of atropine. Therefore, we gave doses of 1.0 mg. of atropine to eight patients with essential hypertension. No significant decreases in blood pressure in the vertical position were found.
Another possible implication of our work is suggested by the observation of Smithwick that four of nine patients with hypertension due to pheochromocytoma had marked postural decrease in blood pressure. Since both Arterenol and epinephrine are present in the blood in such patients, we studied the effect of epinephrine of natural and synthetic origin, with and without the addition of Arterenol. In 21 experiments on eight normal subjects in which hypertension was induced by the continuous intravenous administration of these drugs, there were no significant drops in blood pressure on tilting. We interpret this result to indicate that the postural hypotension which sometimes occurs in patients with pheochromocytoma is not due entirely to circulating epinephrine and/or Arterenol.

**Summary and Conclusions**

1. After atropinization the hypertension induced by Arterenol in human subjects is abolished by tilting to the vertical position. This phenomenon does not occur with equipressor doses of Arterenol alone or with atropine alone. The hypotension on tilting may be prevented by the inflation of blood pressure cuffs on the thighs, with a profound drop in pressure on sudden deflation. Thus, at least part of the drop in pressure appears to be due to pooling of blood in the legs.

2. Experiments on the superior cervical sympathetic ganglion in cats indicated that Arterenol and atropine together do not cause blockade at sympathetic ganglions. Further experiments on dogs showed that these drugs block neither the afferent nor the efferent limbs of the carotid sinus pressor reflex arc. Thus, our observations fail to demonstrate possible sites for interference with the mechanisms for maintenance of arteriolar constriction.

3. In our subjects the clinical observations on tilting did not resemble those in nitrite syncope, in which postarteriolar dilatation is held to be responsible.

4. The administration of atropine to patients with essential hypertension did not induce postural hypotension.

5. Pressor doses of epinephrine of natural and synthetic origin were given intravenously with and without Arterenol to normal subjects. On tilting there were no significant drops in blood pressure.

**References**


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