Measurement of Atropine-Induced Vascular Pooling

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Postural hypotension resulting from 2 mg. of intramuscular atropine appears to be due to peripheral vascular pooling. Controlled studies on 31 normal adult males are reported here and reveal that external compression of the abdomen and lower extremities allows partial cardiovascular compensation. Simultaneous compression of both legs and abdomen is even more effective in preventing postural hypotension. The effects of 2 mg. of atropine appear to be due to partial vagal block, partial ganglionic block and central excitation.

The studies of Gordon and his coworkers,1 and Kalser and associates,2 have demonstrated the development of postural hypotension in a significant number of healthy, young adult males following the intramuscular injection of 2 mg. of atropine sulfate. The most probable explanation for this phenomenon appeared to be vascular pooling in dependent muscle masses and/or the splanchnic bed. The present investigation was undertaken to assess the role of this mechanism in the production of atropine-induced postural hypotension.

EXPERIMENTAL DESIGN

Thirty-one normal adult males were carefully evaluated following the intramuscular injection of 2 mg. of atropine sulfate and comparison was made with similar evaluations following a control injection of isotonic physiologically inactive solution. Twenty of these subjects were studied as regards the effects of vascular pooling on the response to tilting from the horizontal to vertical position.

Each subject, shoeless and dressed in an antiblackout suit,* was placed supine on a tilt table equipped with a foot board and was given 1 cc. of an isotonic physiologically inactive solution. He then rested for 35 minutes, after which blood pressure and pulse were recorded frequently during four successive test periods of 10 minutes each. Each test period was divided into two five-minute phases. The first phase was in the horizontal position and was followed by tilting to 80 degrees and maintenance for five minutes in the vertical position.

At each tilt to the vertical some variant of inflation of the antiblackout suit was instituted during each test period. These included: (1) no inflation of the suit; (2) inflation of the abdominal compartment only; (3) inflation of the lower extremities compartment only; and (4) total inflation of both the abdominal and lower extremities compartments simultaneously. The sequence of inflation was varied between subjects at calculated random. A pressure of 3 pounds per square inch was used to compress the abdomen and lower limbs. This pressure did not occlude the dorsalis pedis pulse nor cause any swelling of the feet.

Immediately after completion of the four test periods with the placebo, each subject was injected intramuscularly with 2 mg. of atropine sulfate in isotonic physiologically inactive solution. The entire procedure was then repeated, the sequence of application of pressure being the same for each subject as during the placebo tests. The subjects were instructed to lie and stand relaxed, but without moving, at all times during the testing.

Blood pressure was recorded by auscultation except when it could not be heard, in which case it was determined by palpation at the radial artery. Pulse was checked at the radial artery for 30-second intervals.

The room was quiet and maintained at a temperature between 70 and 75 F. Placebo and atropine injections were standardized by administration from identical type Ampins.*

RESULTS

Blood Pressure. This dosage of atropine sulfate resulted in a significant alteration of the arterial blood pressure from the placebo response of the 20 subjects.

Following the placebo injection, when no pressure was applied, the diastolic pressure

* Ampins manufactured by Strong Cobb and Company, Inc., Cleveland, Ohio.
showed a considerable and sustained rise with tilting to the vertical, but there was no significant alteration in the systolic pressure (fig. 1). Tilting after external compression of the abdomen or lower extremities resulted in essentially the same response of the systolic and diastolic pressure, although there was a slightly higher diastolic rise during the periods when abdominal compression was applied.

Atropinization caused a marked drop in systolic pressure in all sections with tilting to the vertical position (fig. 2). The greatest initial pressure drop occurred with no compression, whereas, total compression (combined abdominal and lower extremities) resulted in the smallest initial systolic pressure drop. With either abdominal compression, alone, or lower extremity compression, alone, the systolic pressure drop was between these two extremes. The diastolic pressure dropped, with shift to
TABLE 1.—Effect of Body Pressure on Decrease in Blood Pressure and Acceleration of Pulse Rate at Time of Tilting of 20 Normal Adult Males from Horizontal to Vertical Position Following the Intramuscular Injection of 2 mg. Atropine Sulfate

<table>
<thead>
<tr>
<th>Pressure Applied</th>
<th>Effect on Blood Pressure* (mm. Hg)</th>
<th>Effect on Pulse Rate† (per min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>No Pressure</td>
<td>↓ 40 (↓ 4–100)</td>
<td>↓ 13 (↑ 20–72)</td>
</tr>
<tr>
<td></td>
<td>±27.0</td>
<td>±24.8</td>
</tr>
<tr>
<td></td>
<td>↑ 37 (↑ 73–20)</td>
<td>±15.8</td>
</tr>
<tr>
<td>Leg Pressure</td>
<td>↓ 30 (↑ 10–86)</td>
<td>↓ 7 (↑ 24–58)</td>
</tr>
<tr>
<td></td>
<td>±25.0</td>
<td>±21.4</td>
</tr>
<tr>
<td>Abdominal Pressure</td>
<td>↓ 28 (0-92)</td>
<td>↓ 6 (22–52)</td>
</tr>
<tr>
<td></td>
<td>±24.2</td>
<td>±18.9</td>
</tr>
<tr>
<td>Total Pressure</td>
<td>↓ 18 (↑ 4–50)</td>
<td>↑ 1 (↑ 24–32)</td>
</tr>
<tr>
<td></td>
<td>±17.8</td>
<td>±4.6</td>
</tr>
</tbody>
</table>

↓ = fall at time of tilting.
↑ = rise at time of tilting.
* Difference between mean values recorded during first minute after tilting and the preceding horizontal position.
† Difference between greatest mean change occurring during five minute vertical test period and the preceding horizontal position.

TABLE 2.—Comparison of the Effects of 2 mg. Atropine Sulfate and Placebo on Blood Pressure and Pulse of 31 Normal Adult Males Resting Supine for 40 Minutes Following Intramuscular Injection

<table>
<thead>
<tr>
<th>Determination</th>
<th>Atropine*</th>
<th>Placebo*</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure (mm. Hg)</td>
<td>Mean</td>
<td>132</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>96–170</td>
<td>100–146</td>
</tr>
<tr>
<td></td>
<td>St. Dev.</td>
<td>±15.3</td>
<td>±14.3</td>
</tr>
<tr>
<td></td>
<td>Probability</td>
<td>less than .01</td>
<td>less than .01</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mm. Hg)</td>
<td>Mean</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>60–116</td>
<td>55–92</td>
</tr>
<tr>
<td></td>
<td>St. Dev.</td>
<td>±12.8</td>
<td>±9.1</td>
</tr>
<tr>
<td></td>
<td>Probability</td>
<td>less than .01</td>
<td>less than .01</td>
</tr>
<tr>
<td>Pulse Rate (per minute)</td>
<td>Mean</td>
<td>89</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>60–122</td>
<td>54–86</td>
</tr>
<tr>
<td></td>
<td>St. Dev.</td>
<td>±12.7</td>
<td>±7.8</td>
</tr>
<tr>
<td></td>
<td>Probability</td>
<td>less than .01</td>
<td>less than .01</td>
</tr>
</tbody>
</table>

* Each value represents mean of 124 recordings, each subject having been tested four times.

the vertical position, in all instances except with total compression. These results are recorded in table 1.

The resting horizontal blood pressure was significantly higher during the atropine phase than during the placebo phase. Table 2 lists the mean values following placebo and atropine injections. Five individuals showed a marked increase in blood pressure following the 2 mg. of atropine sulfate. Their average systolic increase was 29 mm. Hg and the diastolic increase was 23 mm. Hg.

Pulse Rate. The mean changes in pulse rate following placebo and atropine are recorded in figures 1 and 2. The radial pulse showed a significant rise when the subjects were tilted to the vertical position whether they had had atropine or placebo. However, there was a sinus tachycardia with atropine and the elevation with tilting was approximately twice as great as it was with the placebo. The greatest rise occurred with no compression and the least rise with total compression following either atropine or placebo. Abdominal and lower extremity compression, alone, resulted in a rise intermediary between the other two vertical records. The differences for atropine are shown in table 1.

The mean resting pulse taken 40 minutes after atropinization was significantly higher than the placebo rate (table 2). The average pulse change for the five subjects who had the greatest rise in arterial blood pressure 40
minutes after atropine injection was only 5 beats per minute higher than the average pulse increase for the whole group.

**Syncope.** One atropinized subject went into syncope during the first minute in the vertical position without any external compression. He was immediately lowered to the horizontal position and quickly recovered. There was no previous history of syncope, and he showed a normal response after the placebo injection. Syncope did not result when he was tested with abdominal compression or lower extremity compression, alone. This subject was included in the mean with the other 19 subjects in figures 1 and 2 because he represents an extreme rather than an abnormal reaction to the atropine. His data help to emphasize the effect of external body compression at the various sites. Since only the first value of his vertical no-compression period was obtained, the other mean values recorded during the vertical part of section I of figure 1 represent only 19 subjects and give a slightly higher upsweep to the curve since they did not react as acutely to the atropine.

**Subjective Effects.** The subjects were asked to relate any subjective symptoms or reactions following the injections. All subjects complained of a dry mouth, the time of onset averaging 20 minutes after the atropine injection. There were a few complaints of dull headache, hot flushing of the face, lassitude and mild giddiness or light-headedness. Miosis was minimal and appeared only near the end of the test period. Palpitation was not complained of by any of the subjects. There were no apparent emotional reactions by any of the subjects to the injections.

**Discussion**

These studies have demonstrated that 2 mg. of atropine sulfate given intramuscularly will cause relative postural hypotension in healthy young men within 40 minutes. By the use of external compression applied to the legs and abdomen of atropinized subjects, it has been shown that this results from vascular pooling in the legs and the splanchic area. Changes in arterial blood pressure and pulse rate support this hypothesis.

A comparison of the effects of compression applied to the abdomen or legs separately indicates that the splanchic area and legs are about equally important reservoirs for the vascular pooling associated with atropinization.

This is true when the average results are considered. However, individual cases may show more pooling in one area or the other depending upon undetermined factors. Support of the vascular system by combined abdominal and leg compression is considerably more effective than either leg compression or abdominal compression, alone.

These tests have not elucidated the mechanism by which atropine causes vascular pooling with resultant postural hypotension. However, the results suggest certain sites of action for this drug.

The reaction of these subjects to atropine indicates that there is a partial vagal block (muscarnic) which results in an increase in the resting heart rate. This action of atropine has been well documented.3,5

There is also a significant increase in systolic and diastolic blood pressure. The explanation for this may be the increased pulse which can cause a rise in arterial pressure. This is supported by the fact that the rise in mean systolic pressure is not as great as the rise in mean diastolic pressure. Best and Taylor4 state that pulse rate increases can cause this type of elevation in blood pressure.

However, consideration of individual cases reveals that some subjects had marked elevation in arterial blood pressure with only minimal increases in pulse rate. The five subjects with the greatest blood pressure rise had a systolic pressure increase two and one-half times greater than the entire group and a diastolic increase one and one-half times as much as the average of the other subjects. The same subjects had a pulse increase of only one and two-tenths times the average of the entire group. This indicates that some factor other than tachycardia was acting in some subjects to raise the arterial pressure. This factor may be the action of atropine on the central nervous system. No direct evidence for such a phenomenon was obtained by this investigation. But there are reports of similar
effects on the blood pressure which are attributed to the central excitation by atropine in doses approximating those used here. Bologna,7 Nalefski,8 Myer,9 and Salter3 have reported increased blood pressure and mental disturbances as criteria indicating central nervous system stimulation. The recent work of Himwich10 has clearly shown a comparable effect between central nervous system stimulants and large doses of atropine sulfate in rabbits.

The passive change from supine to standing normally initiates reflex changes in the vascular system which are significantly altered by 2 mg. of atropine. Examination of these alterations further helps to explain the action of this drug.

Approximately 40 minutes after the intramuscular injection of 2 mg. of atropine sulfate, the vascular reflex mechanism is not efficient when the subject is tilted to the standing position. There is an immediate sharp drop in systolic pressure which remains uncompensated for about a minute and then slowly rises to the level of the preatropine pressure. The diastolic pressure drops immediately, but not as much as the systolic pressure. It slowly returns to about the pretilt level of pressure. Compared with the placebo phase, the pulse increases more than twice as much when the atropinized subject is tilted, and it remains faster during the standing period.

Since cardiac acceleration is not impaired when the subject is tilted, the default in reflex action is probably located along the vasopressor pathway. This is substantiated by the fact that in the preatropine subject the diastolic pressure is increased in the standing position, whereas, after atropinization, the diastolic pressure drops immediately after standing and slowly returns to the pretilt level. The best proof of decreased vasopressor tone is vascular pooling, which is partially prevented by external compression of the dependent areas.

Three sites of action may be hypothesized for this atropine effect on the vasomotor reflex: ganglionic, peripheral, or central. Marrazzi11 has shown that large doses of atropine can effectively block transmission by autonomic ganglia and, further, has identified cholinergic and adrenergic mechanisms in the central nervous system.16 The work of Hamet12 suggests that atropine may act directly on the vascular smooth muscle. King13 believes that atropine has central nervous system stimulatory effects, either by direct stimulation of the medullary autonomic centers or by an atropine depression of the higher centers.

Ganglionic blockage would explain postural hypotension during passive standing. However, if ganglionic block, alone, was acting, there should be a relative hypotension even when the subjects were in the supine position. Finnerty14 showed that hexamethonium causes hypotension in supine subjects. Goetz15 reported that pentamethonium did not cause any change in arterial blood pressure when given to subjects in the supine position, but that the subjects did develop hypotension with an increase in pulse rate when standing. Contrary to the action of accepted ganglionic blocking agents, atropine causes a significant relative hypertension in the supine position in the majority of subjects.

Any attempt to explain the action of atropine by a direct effect on the vascular smooth muscle encounters the same difficulty. With direct acting drugs such as amyl nitrite, hypotension has been observed to occur in the supine and standing positions. If atropine had a similar action, there should not be the definite hypertensive trend when the patient is supine.

This action of atropine also cannot be explained on the basis of central stimulation or depression, alone. However, from the preceding discussion, a hypothesis may be suggested that the action of atropine on vasomotor tone is twofold, namely, central excitation and ganglionic blockade. With this hypothesis the supine hypertension may be explained as the result of increased activity in the vasopressor center which causes a relative hypertension in spite of a partial ganglionic block. During passive standing the partial ganglionic block is sufficient to prevent effective vasoconstriction. The result is pooling of blood in the dependent areas of the body.

The use of graded doses of atropine, in larger doses than those employed here, might supply
a more definite answer regarding the exact mechanism of this vascular pooling.

In a recent survey, Gordon and Frye have found that atropine toxicity is rare, but that when it occurs it is frequently due to an atropine sensitivity rather than excessive dosage. The occurrence of syncope in some otherwise normal subjects, although most subjects react only with mild orthostatic hypotension, suggests that measurement of orthostatic hypotension following atropine administration may serve as a test of sensitivity to this drug.

**Summary**

1. It has been determined that the main effect of 2 mg. of atropine sulfate intramuscularly on the cardiovascular system is a decreased vascular tone with pooling in the dependent areas of the body when standing. Pooling occurs in both the splanchnic and peripheral vascular beds.

2. Application of external compression to the abdomen and lower extremities allowed easier cardiovascular compensation for the postural changes. Compression of the legs and abdomen was much more effective than compression of either area, alone.

3. The effects of 2 mg. of atropine demonstrated in this investigation are partial vagal block, partial ganglionic block and central excitation. In the supine position, central excitation and vagal block overbalance ganglionic blockade with a resultant relative hypertension. In the standing position, the ganglionic block is sufficient to prevent adequate vasoconstriction, and there is relative postural hypotension.

**Sumario Español**

1. Se ha determinado que el efecto mayor de 2 mg. de sulfato de atropina intramuscular en el sistema cardiovascular es un decremento en el tono vascular con resultante estancamiento en las partes dependientes cuando el sujeto permanece erecto. El estancamiento ocurre tanto en el cama vascular esplácnica como en la periferal.

2. La aplicación de compresión externa al abdomen y las extremidades inferiores permitió una compensación cardiovascular más fácil para los cambios posturales. La compresión de las piernas y el abdomen fué mucho mas efectiva que la compresión de una de estas áreas a la vez.

3. Los efectos de 2 mg. de atropina demostraron en esta investigación ser, bloqueo vagal parcial, bloqueo gangliónico parcial y excitación central. En la posición reclinada, la excitación central y el bloqueo vagal sobreequilibraron el bloqueo gangliónico con una hipertensión relativa resultante. En la posición erecta, el bloqueo gangliónico es suficiente para evitar vasoconstricción adecuada, y resulta en una hipotensión postural relativa.

**References**


10. Himwich, H. E.: Two behavior effects of atro-

11. Marrazzi, A. S.: Electrical studies on the pharma-

12. Hamet, R.: Sur le mécanisme de l'action vasodila-


