Postural Hypotension Induced by Atropine Sulfate

By Martin H. Kalser, M.D., Ph.D., Charles W. Frye, M.S., and Archer S. Gordon, M.D., Ph.D.

Previous tests on the use of large doses of atropine for the treatment of anticholinesterase poisoning have revealed postural hypotension following the administration of 2 mg. of this drug. In this study on 78 normal adult males, the cardiovascular responses to positional change after 2 mg. atropine have been measured and the mechanisms elucidated. Blood pressure response to tilting was normal during control and placebo phases, but showed a profound alteration after atropine.

The recommended therapy for anticholinesterase intoxication is atropine sulfate and artificial respiration. The use of anticholinesterases as insecticides and their potential use as chemical warfare nerve gas agents has kindled an interest in this well-known parasympatholytic drug and the manual methods of resuscitation.

Atropine sulfate has found a wide range of clinical applications. In most instances it is prescribed in small doses (0.3 mg. to 0.6 mg.). However, it has been established that human tolerance to this drug in the presence of anticholinesterase agents is enormous. Its immediate injection in case of exposure is imperative, and the recommended initial dose is 2 mg.

In civil defense emergencies and possible insecticide exposures, it may become necessary to administer this large dose of atropine to normal, but potentially poisoned, individuals. This possibility has made it desirable to determine the physiologic effects resulting in normal individuals from the intramuscular injection of 2 mg. of atropine sulfate.

Previous reports have detailed the muscular, visual and psychologic effects of doses of atropine up to 3 mg. In a study conducted by this group on 200 normal college men, no serious signs or symptoms were noted following the administration of the recommended initial intramuscular dose. However, hypotension and vertigo were observed in some individuals while they were standing. Accordingly, it seemed appropriate to investigate specific cardiovascular responses of normal adults to the intramuscular injection of 2 mg. of atropine sulfate. In the current study the phenomenon of atropine-induced postural hypotension has been carefully assayed along with an attempt to determine the mechanism of this action.

Methods

The experimental procedure consisted of three phases carried out on a series of 73 normal male military subjects, who were in a random height and weight range and whose average age was under 25 years.

In the first (control) phase, blood pressure, pulse rate, and temperature were recorded before any injection was given. During the second (placebo) phase these same measurements were made from 50 to 70 minutes after a placebo of 1 cc. normal saline was administered intramuscularly. In the third (atropine) phase, determinations were made from 50 to 70 minutes after each subject had received the intramuscular injection of 2 mg. of atropine sulfate in 1 cc. of isotonic physiologically inactive solution.

For the major group of 58 men, the three phases of the study were performed on each individual in the sequence listed above. Each phase included a 10-minute recumbent period immediately followed by a 10-minute period during which the subjects stood "at attention." Active rather than passive change of position was used because it was felt that this would provide a more physiologic test of orthostatic hypotension. In a second group of 15 men, the control phase was omitted and a second 20-minute period was used in both the placebo and atropine

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From the Department of Clinical Science, University of Illinois College of Medicine, Chicago, Ill.

phases to evaluate the effect of exercise during the standing period.

Determinations of blood pressure, pulse rate and skin and oral temperature were made at frequent regular intervals during these periods. Blood pressure was measured by auscultation and heart rate by counting the radial pulse for 30 seconds. An oral thermometer was used to determine body temperature, while skin temperature was measured with a 0 to 100 C. laboratory thermometer held by the subject between his thumb and index finger. The experiments were all completed within three days during the Spring, and the ambient temperature ranged from 72 F. to 84 F., with an average relative humidity of 60 per cent. Both the placebo and the atropine sulfate were given intramuscularly from identical type Ampins.*

Following the placebo phase, all subjects were asked to complete a standard questionnaire† listing possible symptoms. A similar questionnaire was given to the subjects at the end of the atropine phase.

Results

Symptoms (table 1). Approximately 6 per cent of the subjects experienced various symptoms after the injection of the placebo. This group serves to distinguish the psychic effects of the injection, per se, from the pharmacologic effects of the atropine. Following the 2 mg. dose of atropine sulfate, the major symptoms were dryness of mucosal surfaces, visual disturbances, vertigo, flushing and fatigue. Other symptoms included palpitation and paresthesias. Although these symptoms were frequent, in no instance were they found to be more than mildly annoying. Specific psychomotor performance tests were not done, but all subjects were able to cooperate comfortably throughout the studies and returned to their routine activities immediately thereafter.

Oral Temperature. The mean oral temperature in all 73 individuals prior to the injections was 98.6 F., while after the injection the average body temperature was 98.3 F. Although

* Standard Ampins containing 2 mg. of atropine sulfate in 1 cc. of isotonic physiologically inactive solution, and Placebo Ampins containing 1 cc. of isotonic physiologically inactive solution, manufactured by Strong Cobb Co., Cleveland, were furnished by Army Chemical Corps Medical Laboratories.

† Questionnaires were prepared by Dr. Shirley Star and Mr. Frederie Meier, National Opinion Research Center, Chicago, Ill., with careful attention to elimination of suggestion and bias.

the average fall is only 0.3 degrees, this change in body temperature is statistically significant. A fall in postatropine body temperature occurred in 49 subjects, an elevation in 12 and no change in 12. The probability that so many individuals would show a drop in body temperature by chance alone is less than 0.001.

Skin Temperature. The mean skin temperature of the hand in the same 73 subjects prior to atropine was 34.9 C. (94.8 F.), while after the injection it increased to 36.1 C. (97.0 F.). This increase was statistically significant and was noted in 60 subjects while a decrease was seen in four and the remaining nine showed no change.
Blood Pressure (fig. 1 and table 2). A characteristic blood pressure reaction to positional change was noted in the control and placebo phases. In both, the systolic pressure rose 4 mm. Hg immediately after standing and then fell to control levels during the remainder of the erect period. The mean diastolic pressure during the control and placebo phases rose 12 and 10 mm. Hg, respectively, immediately after change of position and increased slightly thereafter. Following atropine, however, the mean blood pressure response to postural change was markedly altered. The systolic pressure, instead of increasing, immediately fell 11 mm. Hg and then increased slightly during the following 10 minutes. The immediate diastolic response was an increase of 5 mm. Hg which was only one-half of the rise seen in the preceding phases. During the 10-minute erect period, the diastolic pressure continued to rise so that the final increase approached that of the control and placebo phases, indicating a delayed diastolic response.

Pulse Rate (fig. 1 and table 2). The mean pulse rate following the placebo was 72 per minute during the supine period and 90 per minute following standing. During the atropine phase, it was 97 and 122 per minute, respectively, in the supine and erect periods. Except for the initial elevation in pulse rate resulting from the atropine, the reaction to change of position was similar in both phases.

Syncope (fig. 2 and tables 3A and 3B). Ten of the 58 subjects for whom three phases were determined developed syncope when they stood after receiving 2 mg. of atropine. Accordingly, they have been considered as a separate group as far as blood pressure and pulse rate data are concerned and have not been included in the above results. Their pulse and blood pressure responses to positional change following the placebo were similar to the responses of the previous group. However, following atropine, syncope developed in each of these cases either immediately or within seven minutes after standing. In evaluation of this data, the last obtainable pulse rate and blood pressure

* The differences in response which have been described are statistically significant.

![Blood Pressure and Pulse Rate Response of Ten Cases in Which Syncope Followed Administration of Atropine](image)(A) Blood pressure and pulse rate response of ten cases in which syncope followed administration of atropine sulfate.

During standing period following atropine the last obtainable pulse (solid dots) and blood pressure (broken vertical lines) before syncope are noted for each individual case. Mean values for last obtainable pulse, 116; last obtainable blood pressure, 84/65.

preceeding the onset of syncope were recorded for each subject. The average of these last blood pressures immediately preceding syncope was 84/65 and the average pulse rate was 116 beats per minute.

Normal, Abnormal and Syncope Responses (table 4). By a modification of the criteria of Eichna, Horvath and Bean,4 blood pressure response to postural change can be classified into three groups on the basis of systolic blood pressure after standing. (1) The normal response shows erect systolic blood pressures above 100 mm. Hg. (2) An abnormal response is characterized by (a) any erect systolic pressure below 100 mm. Hg, and (b) a fall of at least 10 mm. Hg from the lowest supine pressure. (3) The third group includes all cases
POSTURAL HYPOTENSION INDUCED BY ATROPINE SULFATE

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control Phase</th>
<th>Placebo Phase</th>
<th>Atropine Phase</th>
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<tr>
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<td>Standing</td>
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<td>10 minutes</td>
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<td>15 minutes</td>
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<td>97 (84-160)</td>
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<td>5 minutes</td>
<td>117 (98-142)</td>
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<td>110 (94-126)</td>
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<td>7 minutes</td>
<td>116 (98-144)</td>
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<td>109 (94-126)</td>
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<tr>
<td>Standing</td>
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<td>10 minutes (after exercise)</td>
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that develop syncope. Using this classification, 95 per cent of our subjects had a normal reaction in the control and placebo phases, while after atropine less than one-half had normal reactions and 12.5 per cent developed syncope.

Effect of Exercise (fig. 3 and table 5). In the group of 15 subjects, the circulatory effects of a standard exercise were compared after the injection of the placebo and the atropine. The standard exercise consisted of stepping on and off a 14-inch vertical elevation 15 times in 30 seconds immediately after standing, and then remaining standing for 10 minutes.

In this series, the normal response when the erect position was maintained following the standard exercise was an immediate transient increase of the systolic pressure which then returned to normal. The diastolic pressure increased 2 mm. Hg immediately after exercise and continued to rise slowly during the remainder of the 10-minute standing period.

The effect of atropine on the blood pressure response after exercise was a remarkable alteration of this pattern. While standing, immediately after exercise, the mean systolic pressure fell 22 mm. Hg and remained at this low level. Simultaneously, the diastolic pressure fell 12 mm. Hg, but gradually increased during the following 10 minutes to a reading slightly above preexercise levels, the final result being a decrease in the pulse pressure.

Discussion

The normal physiologic response to a change from the horizontal to the vertical stance consists of an initial fall in systolic blood pressure lasting several seconds. This stimulates the carotid sinus and related reflex mechanisms mediated by the autonomic nervous system, with resultant increase in arterial blood pressure and acceleration of the heart.6

Orthostatic hypotension occurs in individuals in whom these reflex mechanisms are hypersensitive and fail to initiate the compensatory blood pressure rise. Various studies have shown that the stress of exhausting exercise, prolonged work or hot baths can accentuate this phenomenon and result in postural hypotension in a significant number of otherwise normal subjects.7 In the latter experiments, peripheral pooling and inadequate venous return were believed to be the principal factors responsible for the failure of normal blood pressure reaction in the erect position.

The current study confirms our previous observations4 that 2 mg of atropine fails to produce serious signs or symptoms in normal adult males, but that an alteration in blood pressure response occurs with change from the supine to the vertical position. It shows further that this effect is enhanced by exercise. An explanation of the exact mechanism of this orthostatic hypotension cannot be made on the basis of either these studies or the usually accepted muscarinic blocking action of atropine. However, there are several other possible hypotheses which will be discussed.

1. With severe tachycardia, decreased ventricular filling can occur as a consequence of significant shortening of diastole, but this does not interfere with cardiac output until the heart rate is at least 180 per minute.8 In our cases, even where syncope occurred after atropine, the average heart rate just prior to collapse was 116 per minute. Thus, it would appear that the atropine-induced tachycardia,


Table 3A — Mean and Range of Temperature, Pulse and Blood Pressure Response Following Change in Position from Lying to Standing, during Control, Placebo and Atropine Phases in 10 Normal Adult Males in Whom Syncope Developed Following the Administration of 2 mg. Atropine Sulfate

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control Phase</th>
<th>Placebo Phase</th>
<th>Atropine Phase</th>
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<td><strong>Oral Temperature (°F.)</strong></td>
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<td>(72-112)</td>
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<td>17 minutes</td>
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<td>(74-116)</td>
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<td><strong>Blood Pressure</strong></td>
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<tr>
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<td>(60-84)</td>
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* See figure 2 and table 3B for individual data.
TABLE 3B.*—Blood Pressure and Pulse Records of Ten Individuals Who Developed Syncope after Standing Following 2 mg. Atropine Sulfate Intramuscularly

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<tr>
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<td>90/72</td>
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<td>62</td>
<td>118/98</td>
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* For mean values of all cases during placebo phase refer to table 3A. Mean of last obtainable pulse rate, 116; mean of last obtainable blood pressure, 84/65.

TABLE 4.—Summary of Systolic Blood Pressure Response to Change in Position from Lying to Standing

| Phase      | Response |                  |              |              |
|------------|----------|------------------|--------------|
|            | Normal*  | Abnormal†        | Syncope‡     |
| Control.... | 93.8%    | 4.2%             | 2.0%         |
| Placebo.... | 96.9%    | 3.1%             | 0.0%         |
| Atropine....| 45.8%    | 41.7%            | 12.5%        |

* Systolic blood pressure above 100 mm. Hg while standing.
† (a) Systolic blood pressure below 100 mm. Hg, and (b) at least 10 mm. Hg fall below lowest control level while standing.
‡ Cases who developed signs and symptoms of collapse with fainting, while standing.

per se, was not responsible for the low blood pressure.

2. Another possible explanation would be an alteration of the normal pressor response to standing resulting from vasodilatation and impaired venous return. Several factors tend to indicate that vasodilatation did occur in these subjects after atropine administration. First, a significant elevation of skin temperature occurred, while body temperature decreased. Also, in those subjects who developed syncope while standing, marked elevation of the systolic and diastolic pressure above their initial levels occurred immediately after lying down. This indicates that with resumption of the supine position, the circulating blood volume increased rapidly as a result of the return of pooled blood to the general circulation.

Vasodilatation of the superficial vessels of the face and neck, the "atropine flush," is well-known, but the mechanism of this cutaneous phenomenon remains controversial. Whether dilatation of cutaneous vessels alone could divert sufficient blood from the effective circulating volume to result in postural hypotension is uncertain. However, it appears improbable that this superficial reservoir can be held responsible for the production of profound hypotension and syncope. The large dependent muscle masses of the extremities and/or the splanchnic bed offer more probable sites for the occurrence of vascular pooling resulting in orthostatic hypotension following 2 mg. of atropine sulfate. Carefully controlled studies have been carried out to support this view and are reported elsewhere.⁹

Although vascular pooling may be incriminated as the mechanism resulting in atropine-induced postural hypotension, the exact mechanism responsible for the pooling remains equivocal. Previous investigators have alternately attributed vascular relaxation following atropine to central depression, ganglionic blockade or terminal action. Although atropine is usually credited only with the role of muscarinic blockade, the studies of Marrazi⁹,¹¹...
TABLE 5.—Mean and Range of Temperature, Pulse and Blood Pressure Response of 15 Normal Adult Males, Following Change in Position from Lying to Standing, and with Exercise upon Standing, during Placebo and Atro-

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Placebo Phase</th>
<th>Atropine Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Temperature (°F.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying</td>
<td>98.6</td>
<td>98.3</td>
</tr>
<tr>
<td>(97.8-99.8)</td>
<td>(97.4-99.4)</td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>98.7</td>
<td>98.4</td>
</tr>
<tr>
<td>(97.8-100.0)</td>
<td>(96.6-99.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin Temperature (°C.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying</td>
<td>33.3</td>
<td>35.1</td>
</tr>
<tr>
<td>(26-37)</td>
<td>(32-37)</td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>32.7</td>
<td>34.9</td>
</tr>
<tr>
<td>(26-36)</td>
<td>(31-37)</td>
<td></td>
</tr>
<tr>
<td><strong>Pulse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 minutes</td>
<td>69</td>
<td>91</td>
</tr>
<tr>
<td>(56-98)</td>
<td>(62-130)</td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>68</td>
<td>93</td>
</tr>
<tr>
<td>(54-96)</td>
<td>(66-126)</td>
<td></td>
</tr>
<tr>
<td>7 minutes</td>
<td>68</td>
<td>94</td>
</tr>
<tr>
<td>(56-98)</td>
<td>(76-120)</td>
<td></td>
</tr>
<tr>
<td>Standing:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 minutes</td>
<td>91</td>
<td>122</td>
</tr>
<tr>
<td>(74-124)</td>
<td>(94-156)</td>
<td></td>
</tr>
<tr>
<td>12 minutes</td>
<td>90</td>
<td>120</td>
</tr>
<tr>
<td>(68-124)</td>
<td>(94-154)</td>
<td></td>
</tr>
<tr>
<td>15 minutes</td>
<td>90</td>
<td>119</td>
</tr>
<tr>
<td>(68-122)</td>
<td>(92-150)</td>
<td></td>
</tr>
<tr>
<td>17 minutes</td>
<td>91</td>
<td>118</td>
</tr>
<tr>
<td>(66-118)</td>
<td>(90-148)</td>
<td></td>
</tr>
<tr>
<td>20 minutes</td>
<td>91</td>
<td>119</td>
</tr>
<tr>
<td>(66-120)</td>
<td>(90-148)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Lying:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 minutes</td>
<td>118</td>
<td>67</td>
</tr>
<tr>
<td>(102-136)</td>
<td>(58-86)</td>
<td>(104-138)</td>
</tr>
<tr>
<td>5 minutes</td>
<td>117</td>
<td>66</td>
</tr>
<tr>
<td>(102-130)</td>
<td>(56-86)</td>
<td>(106-142)</td>
</tr>
<tr>
<td>7 minutes</td>
<td>117</td>
<td>65</td>
</tr>
<tr>
<td>(102-130)</td>
<td>(58-84)</td>
<td>(102-144)</td>
</tr>
<tr>
<td>Standing:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 minutes</td>
<td>127</td>
<td>67</td>
</tr>
<tr>
<td>(after exercise)</td>
<td>(100-152)</td>
<td>(52-90)</td>
</tr>
<tr>
<td>12 minutes</td>
<td>123</td>
<td>72</td>
</tr>
<tr>
<td>(100-138)</td>
<td>(64-99)</td>
<td>(94-140)</td>
</tr>
<tr>
<td>15 minutes</td>
<td>120</td>
<td>73</td>
</tr>
<tr>
<td>(100-134)</td>
<td>(60-94)</td>
<td>(90-138)</td>
</tr>
<tr>
<td>17 minutes</td>
<td>118</td>
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<td>(60-88)</td>
<td>(72-126)</td>
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<td>74</td>
</tr>
<tr>
<td>(100-134)</td>
<td>(62-92)</td>
<td>(88-128)</td>
</tr>
</tbody>
</table>
have attributed a ganglionic blocking action to the drug. It is of interest in this regard that the studies of Brown and coworkers\textsuperscript{12} with a known ganglionic blocking agent, tetraethylammonium chloride, revealed an orthostatic hypotension similar in severity to that observed in the current study. Sollman\textsuperscript{13} mentions Regnier's work indicating that large doses of atropine antagonize the constrictor action of epinephrine. Gyermek\textsuperscript{14} noted a lowering of blood pressure in cats following the administration of atropine, and states that it is due to ganglionic blockade but that this depends upon the sympathetic vasomotor tonus of the animal. Other investigators\textsuperscript{15} have used atropine to abolish the vasoconstriction induced by adrenaline or sympathetic nerve stimulation in the vessels of the rabbit's ear.

Salter\textsuperscript{16} mentions that large doses of atropine depress the central vasoconstrictor center with loss of vascular tone. He further cites the studies and review of Hamet\textsuperscript{17} on the effects of atropine directly at the peripheral level in causing relaxation of vascular smooth muscle.

The development of postural hypotension in human subjects following the administration of 2 mg. of atropine and, apparently, due to pooling in the splanchnic and dependent areas, appears well substantiated. However, conflicting evidence precludes assigning the mechanism to a central, ganglionic or terminal blockade of sympathetic vasoconstrictor tone, or combination of these factors.

**Conclusions**

1. Studies performed on 78 normal adult males reveal that no serious symptoms or physiologic effects result from the intramuscular injection of 2 mg. of atropine sulfate, which is the recommended initial dose following exposure to the anticholinesterase nerve gas agents or insecticides.

2. These subjects have been observed to exhibit a normal blood pressure and pulse rate response to change in position from supine to erect in control studies and following a placebo of 1 cc. of an isotonic physiologically inactive solution. This consisted of a slight rise in systolic pressure, with a gradual return to normal, and a marked rise in pulse rate and diastolic pressure with the elevation being sustained or increasing slightly.

3. Following atropine this normal blood pressure response was altered and was characterized by a profound and sustained fall in systolic pressure with only one-half the previous diastolic rise.

4. A 30-second period of standard exercise at the time of standing enhanced this fall in systolic pressure and resulted in a simultaneous fall in diastolic pressure.

**Sumario Español**

1. Estudios efectuados en 78 adultos varones normales revelaron que luego de la inyección intramuscular de 2 mg. de sulfato de atropina que es la dosis inicial recomendada después de la exposición a agentes de gas anti-colinesterasa nerviosos o insecticidas, no ocurrieron síntomas o efectos fisiológicos serios.

2. Estos sujetos se han observado exhibir una presión arterial normal y pulso como respuesta al cambio en posición de la posición acostada a la erecta en estudios controles y luego de la administración de placebo de 1 cc. de solución isotónica fisiológicamente inactiva. Esto consistió en un ligero aumento en presión sistólica, con un retorno gradual a lo normal y un marcado aumento en el pulso y la presión diastólica con la elevación siendo sostenida o aumentando gradualmente.

3. Luego de la atropina esta respuesta normal de la presión arterial fue alterada y se caracterizó por una profunda y sostenida caída en presión sistólica con solamente la mitad del previo incremento diastólico.

4. Un período de ejercicio uniforme al tiempo de asumir la posición erecta favoreció la caída en presión sistólica y resultó en una caída simultánea en la presión diastólica.

**References**


Postural Hypotension Induced by Atropine Sulfate
MARTIN H. KALSER, CHARLES W. FRYE and ARCHER S. GORDON

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