Effects of Atropine and Isoproterenol on Cardiac Output, Central Venous Pressure, and Mean Transit Time of Indicators Placed at Three Different Sites in the Venous System

By Ralph Gorten, M.D., J. Caulie Gunnell, M.D., Arnold M. Weisser, M.D., and Eugene A. Stead, Jr., M.D.

Both atropine and isoproterenol (Isuprel) increase the cardiac output when given intravenously to normal recumbent subjects.1, 2 In the present investigation, the changes in the circulation induced by these drugs have been studied by simultaneous injection of Evans blue dye (T-1824) into the superior vena cava and radioactive iodinated (T131) human serum albumin into either the antecubital or femoral vein. In addition to defining and comparing some of the actions of these drugs on the circulation, observations were made on the effects of increased cardiac output on the volume and distribution of blood in which the indicator is diluted.

Methods

Twenty studies were performed on normal young male subjects in the supine position and post-absorptive state. In all subjects, a woven silk catheter was introduced into the right antecubital vein and its tip placed in the superior vena cava near the right atrium. This was utilized for injection of Evans blue dye (T-1824) and measurement of central venous pressure. An 18-gauge Cournand needle was then placed in a peripheral vein: a large, freely flowing medial antecubital vein in seven cases and the right femoral vein in 13 cases. This peripheral venous needle was used for the injection of a second indicator, radioiodinated human serum albumin (I131SA) containing 15 to 20 μc of activity in a 1.5- to 2.0-ml volume.

Another 18-gauge Cournand needle was placed in the left brachial artery to serve as a common or single sampling site for the serial collection of timed (two-second) arterial blood samples containing the two simultaneously injected indicators. The serially collected arterial samples were analyzed in the following manner: (1) T-1824 concentration was measured, using a Beckman spectrophotometer, and (2) radioactivity was measured using a well scintillation counter according to the method of Smith and Hooper.3 From the above analyses, using the single series of arterial samples, two time-concentration curves were constructed for the simultaneously injected central and peripheral indicators. The Stewart-Hamilton formula4 was applied to these curves for the determination of cardiac output and mean transit time.

The total blood volume was determined in all subjects using I131SA as the indicator. The sample was drawn 10 minutes after injection.

Pressures in the brachial artery and superior vena cava were recorded by Statham strain-gauge transducers and a multichannel recording unit. The second intercostal space, 5 cm. below the angle of the sternum, was the reference point for all pressure determinations. Peripheral resistance was expressed in arbitrary units obtained by dividing the mean arterial pressure by the cardiac output per minute. Electronic integration was used in measuring the mean arterial and mean central venous pressures. A standard limb lead electrocardiogram was used to measure the heart rate during time of cardiac output determination.

T-1824 was injected into the superior vena cava via the catheter in all subjects. In seven studies with atropine, I131SA was injected through the antecubital vein simultaneously with the central dye. Observations were made in a control state and again one and a half to two minutes after the completion of the intravenous (via catheter) administration of 2 mg. atropine sulfate injected over a one-minute period in a 5-ml volume. In seven other studies with atropine, the same tech-
Hemodynamic Data Before and After Atropine Administration: T-1824 Injected into Superior Vena Cava, IHSA into Antecubital Vein

### Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Blue dye (T-1824)</th>
<th>Well-counter (IHSA)</th>
<th>Peripheral resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CO* (L/min.) MTI (sec.)</td>
<td>CO (L/min.) MTI (sec.)</td>
<td>Heart rate Stroke volume (cc.) MAP/CO CVF (cm. H2O)</td>
</tr>
<tr>
<td>I</td>
<td>B 6.3 14.9  7.7 28.3</td>
<td>66 95 119</td>
<td>+1.34</td>
</tr>
<tr>
<td>II</td>
<td>A 9.2 10.1  9.3 19.2</td>
<td>126 73 93</td>
<td>-1.33</td>
</tr>
<tr>
<td></td>
<td>B 5.4 16.5  6.7 29.2</td>
<td>74 86 128</td>
<td>0.0</td>
</tr>
<tr>
<td>III</td>
<td>A 8.6 11.3  9.1 17.7</td>
<td>128 69 105</td>
<td>-3.78</td>
</tr>
<tr>
<td></td>
<td>B 5.8 16.0  5.8 36.9</td>
<td>69 84 134</td>
<td>+1.34</td>
</tr>
<tr>
<td>IV</td>
<td>A 8.2 11.3  8.4 20.6</td>
<td>125 65 98  -0.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 5.4 17.7  5.3 34.6</td>
<td>60 90 119</td>
<td>+4.90</td>
</tr>
<tr>
<td>V</td>
<td>A 8.2 10.6  8.4 18.1</td>
<td>111 74 105</td>
<td>-2.33</td>
</tr>
<tr>
<td></td>
<td>B 6.5 14.6  6.3 24.5</td>
<td>72 90 105</td>
<td>+0.81</td>
</tr>
<tr>
<td>VI</td>
<td>A 9.7 12.4  10.0 17.6</td>
<td>100 97 77</td>
<td>-1.34</td>
</tr>
<tr>
<td></td>
<td>B 6.3 15.2  5.9 35.1</td>
<td>66 95 135</td>
<td>+4.00</td>
</tr>
<tr>
<td>VII</td>
<td>A 8.5 11.9  8.3 22.6</td>
<td>123 69 96</td>
<td>+1.33</td>
</tr>
<tr>
<td></td>
<td>B 6.0 16.4  6.1 32.5</td>
<td>67 90 124</td>
<td>+2.02</td>
</tr>
<tr>
<td>Mean</td>
<td>A 8.6 11.3  8.8 19.0</td>
<td>120 72 96</td>
<td>-1.12</td>
</tr>
</tbody>
</table>

*CO = Cardiac output.  
1MTT = Mean transit time.  
2MAP = Mean arterial pressure.  
§CVP = Central venous pressure.

Results

When the indicator was injected into a femoral or antecubital vein, the calculated value for cardiac output tended to be greater than when the indicator was injected into the superior vena cava. The difference was usually small and assumed statistical significance only in a large series. With peripheral injection, a variable portion of the indicator injected does not reach the heart in time to be included in the initial portion of the curve from which the output calculation is made. The statistical treatment of all our data on peripheral and central injections has been discussed elsewhere. The calculated increase in cardiac output produced by the two drugs was the same when the observations were made from the same injection site before and after the drugs.

Atropine (tables 1 and 2) in the dosage given increased the mean heart rate from 65 to 113 beats per minute. The mean increase in cardiac output was 2.5 L/min. The heart rate increased relatively more than the cardiac output. This increase resulted in a fall in stroke volume. The total blood volume was unchanged. The arterial systolic pressure rose slightly in nine of the 14 subjects, and the average diastolic pressure rose 12 mm. Hg. The calculated peripheral resistance decreased in all subjects, and the average fall in central venous pressure was 3.3 cm. H2O.

Isoproterenol (table 3), in the dosage used, produced approximately the same degree of rise in cardiac output and a slightly smaller mean fall in central venous pressure than did the atropine. In contrast to atropine, the stroke volume rose significantly with isopro-
ATROPINE AND ISOPROTERENOL

Table 2
Hemodynamic Data Before and After Atropine Administration: T-1824 Injected into Superior Vena Cava, IHSA into Femoral Vein

<table>
<thead>
<tr>
<th>Subject</th>
<th>Blue dye (T-1824)</th>
<th>Wall-counter (IHSA)</th>
<th>Peripheral resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COa (L/min.)</td>
<td>MTTt (sec.)</td>
<td>COa (L/min.)</td>
</tr>
<tr>
<td>I</td>
<td>6.7</td>
<td>19.5</td>
<td>6.7</td>
</tr>
<tr>
<td>A</td>
<td>8.8</td>
<td>15.2</td>
<td>8.5</td>
</tr>
<tr>
<td>B</td>
<td>5.8</td>
<td>14.3</td>
<td>5.8</td>
</tr>
<tr>
<td>II</td>
<td>8.4</td>
<td>8.9</td>
<td>8.2</td>
</tr>
<tr>
<td>A</td>
<td>5.8</td>
<td>20.7</td>
<td>6.6</td>
</tr>
<tr>
<td>III</td>
<td>9.1</td>
<td>12.5</td>
<td>10.1</td>
</tr>
<tr>
<td>A</td>
<td>5.3</td>
<td>17.5</td>
<td>6.6</td>
</tr>
<tr>
<td>IV</td>
<td>7.4</td>
<td>11.9</td>
<td>8.6</td>
</tr>
<tr>
<td>B</td>
<td>6.8</td>
<td>12.8</td>
<td>7.2</td>
</tr>
<tr>
<td>V</td>
<td>7.6</td>
<td>9.8</td>
<td>5.3</td>
</tr>
<tr>
<td>A</td>
<td>5.7</td>
<td>16.1</td>
<td>6.1</td>
</tr>
<tr>
<td>B</td>
<td>7.8</td>
<td>10.9</td>
<td>8.1</td>
</tr>
<tr>
<td>B</td>
<td>3.9</td>
<td>20.2</td>
<td>3.6</td>
</tr>
<tr>
<td>VII</td>
<td>7.6</td>
<td>12.3</td>
<td>6.8</td>
</tr>
<tr>
<td>A</td>
<td>5.7</td>
<td>17.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Mean</td>
<td>8.1</td>
<td>11.6</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*CO = Cardiac output.
†MTT = Mean transit time.
‡MAP = Mean arterial pressure.
§CVP = Central venous pressure.

*CO = Cardiac output.
†MTT = Mean transit time.
‡MAP = Mean arterial pressure.
§CVP = Central venous pressure.

The mean stroke volume before isoproterenol was 83 ml.; the mean stroke volume after the drug was 105 ml. The mean pulse rate increased nine beats per minute, and the average mean arterial pressure fell 4 mm. Hg. In all subjects, the systolic pressure increased, while the diastolic pressure fell. The decrease in peripheral resistance with isoproterenol was more marked than with atropine. The total blood volume was unchanged.

The cardiac output and mean transit time measurements from the peripheral vein and superior vena cava were compared before and after the administration of atropine and isoproterenol. When the dye was injected into the superior vena cava, the increased cardiac output produced by the drugs had no effect on the peak concentration of the dye collected from the artery. The shortening of the mean transit time was proportional to the increase in cardiac output. These relationships were different when the indicator was injected into the antecubital or femoral veins. At both peripheral sites, the administered drugs caused a rise in peak concentration of the indicator in the samples collected from the artery and a shortening of the mean transit time out of proportion to the increase in cardiac output.

Discussion
The change in mean central venous pressure was definitely related to the administration of a drug. The magnitude of the fall clearly separated the action of the drug from the spontaneously occurring changes in central venous pressure.

With atropine there were no observed changes in respiratory rate or depth to suggest that the decrease in central venous pressure resulted from an increase in negative pressure within the thorax. Isoproterenol, however, does increase ventilation. Eckstein and Hamilton⁶ have shown that the fall in atrial pressure produced by isoproterenol is not accompanied by a fall in esophageal pressure, and from this they conclude that a fall in intrapleural pressure cannot account for the observed decrease in central venous pressure. From our studies, the irregular and
Table 3

<table>
<thead>
<tr>
<th>Subject</th>
<th>Blue dye (T-1824)</th>
<th>Well-counter (IIHA)</th>
<th>Peripheral resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CO* (L./min.)</td>
<td>MTT† (sec.)</td>
<td>CO* (L./min.)</td>
</tr>
<tr>
<td>I</td>
<td>5.0</td>
<td>18.1</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>12.3</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>4.7</td>
<td>20.9</td>
<td>5.2</td>
</tr>
<tr>
<td>II</td>
<td>6.9</td>
<td>15.3</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>5.7</td>
<td>10.2</td>
<td>6.5</td>
</tr>
<tr>
<td>III</td>
<td>5.2</td>
<td>12.4</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>5.7</td>
<td>14.6</td>
<td>6.5</td>
</tr>
<tr>
<td>IV</td>
<td>6.9</td>
<td>13.4</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>18.2</td>
<td>6.8</td>
</tr>
<tr>
<td>V</td>
<td>8.9</td>
<td>10.7</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>20.1</td>
<td>5.1</td>
</tr>
<tr>
<td>VI</td>
<td>6.7</td>
<td>13.3</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>5.2</td>
<td>18.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Mean</td>
<td>7.6</td>
<td>12.5</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Minimal changes in blood volume and the rapidity of the change in central venous pressure following the administration of the drugs indicate that changes in total blood volume are not of primary importance. The fall in central venous pressure is compatible with either a change in the pressure volume characteristics of the venous system, or redistribution of blood within the vascular system, or a combination of these two.

The atropine-induced rise in cardiac output was associated with an increase in pressure gradient between the arterial system and the superior vena cava. With isoproterenol, the gradient was either unchanged or slightly decreased.

It is of interest that the central venous pressure was lower in the presence of an increased cardiac output and that this relationship was present both with atropine, which increased mean arterial pressure and lowered stroke volume, and with isoproterenol, which lowered mean arterial pressure and increased stroke volume. From the present data, one cannot ascertain whether the peripheral flow or the cardiac output increased first or whether both changes occurred together. The fall in peripheral resistance with the rise in cardiac output indicated that the overall response to both drugs was one of vasodilatation. The increase in capacity of the system in the vascular beds where vasodilatation occurred may be sufficient to account for the observed fall in central venous pressure.

The response of the heart to the two drugs was similar in that the rise in output was of the same order of magnitude, but the method of adaptation resulting from the rise in output was quite different. With atropine, the ventricles received less blood during each diastole; with isoproterenol, the ventricles received more blood with each diastole. In both instances, the right ventricle had no difficulty in moving forward a greater volume of blood with a lower mean central venous pressure.

From examination of the data, we can conclude that changes occurred in the periphery and in the heart, that the change in the periphery was that of overall vasodilatation, that the heart was able to accept more blood per minute with a decreased central venous pressure, and that, depending on the situation,
the heart could vary its output by increasing
the stroke volume or by increasing the rate
without an increase in stroke volume. From
these data, collected at two periods of circula-
tory equilibrium, we cannot define the events
occurring in passing from one state to another.
We cannot separate primary effects on cardiac
output with secondary peripheral vasodilata-
tion from primary effects on peripheral vaso-
dilation with secondary increases in cardiac
output. We do not know to what degree the
first increase in output is dependent on in-
creased venous return, even though we know
that a sustained increase in output must de-
pend on a sustained increase in venous return.

In a given subject, changes in the mean
transit time between the superior vena cava
and the brachial artery were proportional to
changes in cardiac output. The fact that the
indicator can be moved more rapidly from
the superior vena cava through both chambers
of the heart and the pulmonary circulation to
the point of arterial sampling without increas-
ing the diluting volume or changing the peak
concentration is of interest. It suggests that
the increase in flow is accomplished without
much change in the relative pattern of flow
in the areas traversed. The possibility that
a change in the diluting volume in the lung
occurred and was masked by a change in dis-
tribution of the pattern of arterial flow can-
not be excluded by these data.7,8

With peripheral injection of the indicators,
changes in mean transit time caused by the
drugs were not proportional to the changes in
cardiac output. Increasing the cardiac output
caused an increase in the peak concentration
of the indicator in the blood from the brachial
artery. These data suggest that both drugs
produced changes in the patterns of periph-
eral blood flow.

Summary

Two milligrams of atropine given intrave-
nously increased the cardiac output, the mean
arterial pressure, and the heart rate and low-
ered the central venous pressure, stroke out-
put, and peripheral resistance. Isoproterenol
given intravenously at the rate of 1 μg. per
minute increased the cardiac output with only
an average increase in pulse rate of nine beats
per minute. The stroke volume was increased.
The central venous pressure and the periph-
eral resistance were decreased. These observa-
tions on the circulation were made in the
steady state. They demonstrate that the min-
ute output of the heart can be increased by
either a rise in rate or an increase in stroke
volume in the presence of a fall in central
venous pressure. They do not define the order
of events leading to the steady state. When
the indicator was placed in the superior vena
cava, neither atropine nor isoproterenol
changed the volume in which the indicator
was diluted during its first circulation. Both
atropine and isoproterenol decreased the vol-
umes in which the indicators were diluted
when they were injected into the antecubital
or femoral veins.

References

1. WEISSLER, A. M., LEONARD, J. J., AND WARREN,
   J. V.: Effects of posture and atropine on
2. WARREN, J. V., WEISSLER, A. M., AND LEONARD,
   J. J.: Observation of determinants of cardiac
3. SMITH, J. R., AND HOOPLE, J. W.: Acute and
   chronic cardiovascular effects of penicillin in
   hypertensive patients. Circulation 14: 1061,
   1956.
4. HAMILTON, W. F., MOORE, J. W., KINSMA,
   J. M., AND SPURLING, R. B.: Studies on circu-
lation: IV. Further analysis of injection
   method and of changes in hemodynamics under
   physiological and pathological conditions. Am.
5. GUNNELS, J. C, AND GORSEN, R. J.: Effect of
   varying indicator injection sites on values for
   cardiac output. J. Appl. Physiol. 16: 261,
   1961.
6. ECKSTEIN, J. W., AND HAMILTON, W. K.: Effects
   of isoproterenol on peripheral venous tone
   and transmural right atrial pressure in man.
7. GLEASON, W. L., BACOS, J. M., MILLER, D. E.,
   AND MCLINTOSH, H. D.: Major pitfalls in
   Res. 7: 227, 1959.
8. MARSHALL, R. J., AND SHEPHERD, J. T.: Inter-
   pretation of changes in "central" blood volume
Effects of Atropine and Isoproterenol on Cardiac Output, Central Venous Pressure, and Mean Transit Time of Indicators Placed at Three Different Sites in the Venous System
RALPH GORTEX, J. CAULIE GUNXELLS, ARNOLD M. WEISSLER and EUGENE A. STEAD, Jr.

doi: 10.1161/01.RES.9.5.979

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1961 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/9/5/979