THE EFFECT OF MORPHINE ON THE CARDIOVASCULAR SYSTEM OF THE DOG ANESTHETIZED WITH CYCLOPROPA N

LAWRENCE G. SCHULL, M.D., GEOFFREY BERRY, M.D., ROBERTO VILLABRECAL, M.D., JOHN THOMAS, M.D.

The effect of anesthetic agents on the cardiovascular system is of great importance to anesthesiologists. Of equal importance is the similar effect of drugs used for premedication or given intravenously during anesthesia. The purpose of this work is to determine the effect of morphine and atropine on the cardiovascular system of dogs anesthetized with cyclopropane.

Robbins and Baxter and Greisheimer and associates found that unanesthetized dogs when anesthetized with cyclopropane had increased cardiac indices over those dogs in the unanesthetized state. Greisheimer and associates found that in intact dogs premedicated with morphine, cyclopropane anesthesia caused a decrease in cardiac index over that obtained in the unanesthetized animal.

Prime and Gray and Price and Helrich found the cardiac index decreased markedly when cyclopropane and all other anesthetic agents studied were added to the heart-lung preparation. In man premedicated with morphine and anesthetized with cyclopropane, cardiac index has been found to be decreased from that in the awake state by all investigators. In man premedicated with chlorpromazine, Etsten and Li found the cardiac index to be increased, and when man was premedicated with morphine, the cardiac index was decreased. In the most recent work, Jones, Guldman and co-workers found that in unpremedicated man, cardiac output was increased, along with arterial pressure and right atrial pressure. If morphine was given preoperatively there was a decrease in the cardiac output during the administration of cyclopropane.

Accepted for publication November 15, 1960. The authors are in the Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, Tennessee. This study was begun by Benjamin H. Robbins, M.D., Professor of Anesthesiology, Vanderbilt University School of Medicine, prior to his death.

Methods

Mongrel dogs varying in weight from 8 to 18 kg were used for the study. Cardiac output was determined using the dye dilution technique. This was carried out using a Waters oximeter cuvette and tricarbocyanide dye as presented by Fox and co-workers. The output was recorded on a Grass multichannel recorder along with arterial pressure (via Statham strain gauge), electroencephalogram, and electrocardiogram. Arterial blood samples were taken using oiling, sealed syringes. Cyclopropane, oxygen and carbon dioxide contents were determined on these samples using the Van Slyke apparatus and the method of Orcutt and Waters. Respiratory was assisted when pulmonary ventilation appeared inadequate; following the injection of morphine intravenously, the dogs became apneic and respiration was controlled.

These animals were divided into two groups: In group 1, 5 dogs had cannulations of the external jugular vein and femoral artery carried out under local anesthesia and cardiac output was determined prior to anesthetization. These dogs were then anesthetized with cyclopropane and a steady state reached. This was approximately 40 minutes after induction of anesthesia. Five other animals were anesthetized with cyclopropane and while a steady state was being reached, cannulations of the external jugular vein and femoral artery were carried out. Cardiac output was then determined in these anesthetized animals in light surgical and deep surgical anesthesia. Then morphine was given intravenously in a dosage of 1 mg. per kilogram and after 30 minutes cardiac index was determined. Twenty minutes following this cardiac output, atropine, 3 mg., was given intravenously and the cardiac output again determined.

In group 2, 3 mg. per kilogram morphine was given to 3 dogs intramuscularly. Follow-
ing the defecation reflex, anesthesia was induced with cyclopropane. Cardiac outputs were determined in levels of light and deep surgical anesthesia. Each dog was then given a narcotic antagonist, levallorphan, 3 mg. intravenously. Ten minutes after this, cardiac output was determined at the same depth of anesthesia and at a deeper level of anesthesia. In both series, after cardiac output was determined, the blood was reinfused into the animal to prevent decreasing the circulating blood volume.

RESULTS

The results on group 1 animals are shown in table 1. In a series of five trials the cardiac index of the unanesthetized dog was 2.8 l./minute/m.² ± .16 (S.E.). When anesthesia had been induced and a cyclopropane concentration of 16.2 mg. per cent established, cardiac index decreased to 2.41 ± .10 which is a statistically significant change. When anesthesia was deepened to a level of 21 mg. per cent of cyclopropane, the cardiac index declined to 1.99 ± .15 which again is statistically significant. Following the intravenous morphine, there was a pronounced decrease of the cardiac index to 1.28 l./minute/m.² of body surface. After the injection of atropine, cardiac index increased to 2.43 ± .18 which is a highly significant change from that obtained following intravenous morphine.

Heart Rate. There was no statistically significant change in the heart rate from that observed in the unanesthetized animals of 103 ± 4 until following the intravenous injection of morphine at which time the pulse rate decreased to 56 ± 7. The injection of atropine caused an increase in pulse rate to 140 ± 4, a significant increase from that following morphine and that of the unanesthetized animal. There were no arrhythmias produced.

Stroke Index. There was a significant change in the stroke index from 27.3 cc./m.² in the unanesthetized animal to 21.3 ± 1.5 which was obtained with a cyclopropane concentration of 16.2 mg. per cent. There was no further statistically significant change until a drop to 17.6 cc./m.² ± 1.6 following the injection of intravenous atropine.

Total Peripheral Resistance. When the blood level of cyclopropane was 16.2 mg. per cent, the peripheral resistance was significantly increased from 7,100 ± 400 dyne-second/cm.₅ in the unanesthetized animal to 7,500 ± 500 dyne-second/cm.₅. There was no further significant change until following the intravenous injection of morphine when

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>CHANGES IN CARDIAC INDEX, HEART RATE, STROKE VOLUME, MEAN ARTERIAL PRESSURE AT VARYING CONCENTRATIONS OF CYCLOPROpane FOLLOWING INTRAVENOUS MORPHINE AND ATROPINE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Anesthesia Stage</th>
<th>Post-Morphine</th>
<th>Post-Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>III₇</td>
<td>III₉</td>
</tr>
<tr>
<td>CO₂ (volumes per cent)</td>
<td>40.6</td>
<td>45.2</td>
<td>45.9</td>
</tr>
<tr>
<td>O₂ (volumes per cent)</td>
<td>18.2</td>
<td>17.9</td>
<td>18.1</td>
</tr>
<tr>
<td>C₃H₆ (mg.)</td>
<td>16.2</td>
<td>21.0</td>
<td>17.8</td>
</tr>
<tr>
<td>Number of trials</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac index (l./minute/m²)</td>
<td>2.82 ± 0.16</td>
<td>2.41 ± 0.10</td>
<td>1.99 ± 0.15</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>103 ± 4</td>
<td>118 ± 10</td>
<td>100 ± 17</td>
</tr>
<tr>
<td>Stroke volume index (cc./m³)</td>
<td>27.3 ± 1.3</td>
<td>21.2 ± 1.5</td>
<td>21.2 ± 3.0</td>
</tr>
<tr>
<td>Number with measurements</td>
<td>3</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Blood pressure (mm. Hg)</td>
<td>193/98</td>
<td>178/101</td>
<td>158/80</td>
</tr>
<tr>
<td>Mean pressure (mm. Hg)</td>
<td>140 ± 8</td>
<td>140 ± 4</td>
<td>123 ± 7</td>
</tr>
<tr>
<td>Total peripheral resistance (dyne-second/cm²)</td>
<td>7,100 ± 400</td>
<td>7,500 ± 500</td>
<td>7,800 ± 800</td>
</tr>
</tbody>
</table>

(Mean ± S.E.).
TABLE 2

<table>
<thead>
<tr>
<th>Anesthesia Stage</th>
<th>IIIt-1</th>
<th>Post-Levallophan III2</th>
<th>Post-Levallophan III3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂ (volumes per cent)</td>
<td>56.5</td>
<td>42.2</td>
<td>43.3</td>
</tr>
<tr>
<td>O₂ (volumes per cent)</td>
<td>17.5</td>
<td>18.8</td>
<td>21.3</td>
</tr>
<tr>
<td>C₃H₈ (mg.)</td>
<td>16.1</td>
<td>18.1</td>
<td>21.1</td>
</tr>
<tr>
<td>Cardiac index (l/minute/m²)</td>
<td>1.37±.41</td>
<td>2.38±.31</td>
<td>2.05±.44</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>54±3</td>
<td>149±15</td>
<td>152±5</td>
</tr>
<tr>
<td>Stroke volume index (cc./m²)</td>
<td>25.2±3.1</td>
<td>16.2±2.0</td>
<td>13.7±3.3</td>
</tr>
<tr>
<td>Blood pressure (mm. Hg)</td>
<td>183/80</td>
<td>177/93</td>
<td>190/107</td>
</tr>
<tr>
<td>Mean pressure (mm. Hg)</td>
<td>132±17</td>
<td>135±14</td>
<td>148±4</td>
</tr>
<tr>
<td>Total peripheral resistance (dyne-second/cm²)</td>
<td>13,800±2,100</td>
<td>8,200±1,600</td>
<td>11,300±3,000</td>
</tr>
</tbody>
</table>

(Mean ± S.E.).

there was a marked increase in the peripheral resistance to 13,200 ± 2,000 dyne-second/cm². Following the injection of intravenous atropine there was a decrease in peripheral resistance to a value which was not statistically significant from that obtained in the unanesthetized animal.

Arterial Blood Pressure. There was no significant change in blood pressure with the changing levels of anesthesia.

The results obtained in the second group of animals given morphine prior to induction of anesthesia are shown in table 2. The small number of trials in this group makes statistical interpretation difficult. The cardiac indices obtained in these animals were similar to those obtained in animals given morphine intravenously and having a corresponding concentration of cyclopropane. The change in pulse rate and peripheral resistance are similar. Following intravenous levallophan the changes in cardiac index, pulse rate and peripheral resistance are similar to those resulting from atropine given intravenously in group 1.

**Discussion**

The percentage changes in the cardiac index, heart rate, stroke index, total peripheral resistance and blood pressure from those obtained in the unanesthetized animal are shown graphically in figure 1. The levels of 16.2 and 21 mg. per cent are compatible with moderate to deep surgical anesthesia according to both the classification of Robbins,14,15 and to the electroencephalographic data of Possati and co-workers. The decreased cardiac index which we found

![Percentage changes in heart rate, cardiac index, stroke index and peripheral resistance in dogs anesthetized with cyclopropane and given morphine and then atropine intravenously.](image-url)
with increasing concentrations of cyclopropane are similar to those reported by other investigators.\textsuperscript{6, 10} Prime and Gray\textsuperscript{4} and Thompson and co-workers\textsuperscript{5} and Shackman\textsuperscript{17} found that both the duration and the increasing depth of anesthesia were factors in decreasing the cardiac index.

Our results differ from those of Robbins and Baxter\textsuperscript{1} in that they found the cardiac output increased in 9 unpremedicated dogs under moderate surgical anesthesia, normal in 4 dogs in deep anesthesia and decreased in 5 dogs in deep anesthesia. The chief difference in our work and theirs is the higher pulse rates they recorded for corresponding concentrations of cyclopropane. It would seem that the increased cardiac output reported was due to the higher pulse rate in their series than in ours. In our work we found that when the pulse rate slowed, as was shown with morphine, the cardiac output decreased markedly, and when the pulse rate increased, the output rose to more normal values. Our work differs from that of Jones and co-workers\textsuperscript{11} in the following aspects: (1) Our observations were from dogs and theirs from man. (2) In their work, they found that until the end-expired cyclopropane concentration was 17–20 volumes per cent, the cardiac output was increased in unpremedicated man. Our work agrees with theirs in that when morphine was given to their subjects as preoperative medication, the cardiac output was significantly decreased when cyclopropane anesthesia was administered. Our findings also agree with theirs in that, as shown in table 1, after atropine was given, the $P_{\text{CO}_2}$ was higher than that occurring when the animal developed respiratory depression from morphine.

In our series, we found that with cyclopropane, the total peripheral resistance was increased significantly. It has been commented upon both by Etsten and Li\textsuperscript{9} and by Thompson, Patrick and Wood\textsuperscript{8} that the changes in the total peripheral resistance and the pulse rate with cyclopropane are similar to those produced with norepinephrine infusion. Price and associates\textsuperscript{19} have reported that in man there is an increase in epinephrine and norepinephrine blood levels with cyclopropane anesthesia. It would seem that in the presence of increased norepinephrine and epinephrine levels, there would be a stimulation of cardiac activity. However, as indicated by Richardson, Woods and Richardson,\textsuperscript{19} a depressant effect of the anesthetic on the myocardium with deep anesthesia, might offset any stimulation from an increase of epinephrine and norepinephrine. When morphine was given intravenously, there was a dramatic slowing of the pulse and a decrease in the cardiac index with some slight increase in the stroke index. It would seem that the marked increase in peripheral resistance is associated with the intravenous injection of morphine might indicate some adrenergic effect of morphine. That morphine has some adrenergic action has been shown by Elliott,\textsuperscript{20} Bodo, CoTui and Benaglia,\textsuperscript{21} Housay and Molinelli.\textsuperscript{22} The effect of atropine alone in increasing the cardiac index has been shown by McMichael and Sharp-Schaper\textsuperscript{23} to be due to the increase in heart rate. At the same time that this increase in rate occurred, there was a decrease in right auricular pressure. If this decrease in right auricular pressure was great, there was no change in cardiac index. When the atropine was given in our series, there was a marked increase in rate with a decrease in stroke index and a return of the total peripheral resistance toward control levels obtained in the unanesthetized animal.

In the second group of dogs given morphine intramuscularly prior to induction of anesthesia, the decreased cardiac index and the decrease in pulse rate were similar to those following the intravenous injection of morphine and with a similar concentration of cyclopropane. The use of levallorphan in each case caused an increase in the cardiac index and pulse rate and a decrease in the peripheral resistance. The numbers in this study are too small to make any accurate statistical analyses. However, the trend seemed to indicate that in addition to having a competitive action with morphine on the respiratory center, at least in the dog, there may be an additional competitive action at the vasomotor center.

Eckenhoff, King and Elder\textsuperscript{24} reported that $n$-allylmorphone counteracted the respiratory and vascular depression of morphine.
Also, Smith, Lehman and Gilliafian 25 stated that dogs having n-allylmorphine no longer exhibited the symptoms of the respiratory depression—bradycardia, hypothermia and myosis.

**Summary**

We have determined the effect of morphine given intravenously and intramuscularly to dogs anesthetized with cyclopropane. With increasing depth of anesthesia, cardiac index was decreased and peripheral resistance increased significantly. In those dogs given morphine intravenously, there was a highly significant decrease in pulse rate and a markedly significant decrease in cardiac index and increase in total peripheral resistance which returned to pre-existing levels following intravenous atropine. In those animals given morphine intramuscularly prior to induction of cyclopropane anesthesia, the changes were of the same degree with decreased cardiac index, markedly increased peripheral resistance and bradycardia with a corresponding concentration of cyclopropane. In this instance, the cardiac index, peripheral resistance and pulse rate were returned to prior levels following the use of levallorphan.

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morphine, methadone derivatives and isoni-

SPINAL FLUID CIRCULATION Anes-
ethetized cats were held in a prone position
with the vertebral canal horizontal. Dye
was introduced under standard conditions
into the subarachnoid space at the first sacral,
eleventh thoracic or seventh cervical vertebral
level. The animals were killed within 10
minutes, at 85 minutes or 4 hours after dye
injection. Half of the 85 minute series re-
ceived picrotoxin sufficient to produce convu-
ulsions during the last 30 minutes. After
death the animals were rapidly frozen in the
horizontal position and sectioned transversely
to determine the limits of dye spread. Even
after 4 hours the dye had moved only slightly
from its site of introduction, but much greater
movement was induced by picrotoxin con-
volusions. It is concluded that there is little
circulation of cerebral spinal fluid in the
spinal subarachnoid space of the horizontal
anesthetized cat. However, movement of the
fluid in this space is markedly increased by
picrotoxin convulsions. (Grundy, H. F.: Move-
ment of a Dye in the Spinal Subarach-
noid Space, J. Physiol. 153: 590 (Sept.)
1960.)

INTRATHecal METHYLENE BLUE
Although 1 per cent aqueous methylene blue
has been much used intravenously in the
 treatment of methemoglobinemia without
deleterious effect; and although it has been
injected into the dilated ventricles associated
with cerebrospinal fluid block without obvious
catastrophe (harmful effects may be con-
cealed by the concomitant craniotomy), its
introduction into the lumbar subarachnoid
space is dangerous. Fourteen cases have
been tabulated in which neurological deficits
of varying degree, ranging from mild para-
paresis through quadriplegia, multiple cranial
nerve involvement, obstructive hydrocephalus,
and dementia, have been observed following
its intrathecal use. Once injected, the dye
appears to become fixed to neural tissue.
Sporadic efforts to drain and irrigate the
spinal subarachnoid spaces have not amelio-
rated the situation. Clearly, the use in pa-

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