

THE EFFECT OF MORPHINE ON THE CARDIOVASCULAR SYSTEM OF THE DOG ANESTHETIZED WITH CYCLOPROPANE

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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 Baxter¹ and Greisheimer and associates² found that unpremedicated dogs when anesthetized with cyclopropane had increased cardiac indices over those dogs in the unanesthetized state. Greisheimer and associates³ 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 Gray⁴ and Price and Helrich⁵ 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.⁶⁻⁹ In man premedicated with chlorpromazine, Etsten and Li¹⁰ 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-workers¹¹ 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 tricarbo cyanide dye as presented by Fox and co-workers.¹² The output was recorded on a Grass multi-channel recorder along with arterial pressure (via Statham strain gauge), electroencephalogram, and electrocardiogram. Arterial blood samples were taken using oiled, 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.¹³ Respiration 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 reinjected 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 $2.8 \text{ l./minute/m}^2 \pm .16$ (S.E.). When anesthesia had been induced and a cyclopropane concentration of 16.2 mg. per cent established, cardiac index decreased to $2.41 \pm .10$ 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 $1.99 \pm .15$ which again is statistically significant. Following the intravenous morphine, there was a pronounced decrease of the cardiac index to $1.28 \text{ l./minute/m}^2$ of body surface. After the injection of atropine, cardiac index increased to $2.43 \pm .18$ 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 $17.6 \text{ cc./m}^2 \pm 1.6$ 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 $7,100 \pm 400$ dyne-second/cm.⁵ in the unanesthetized animal to $7,500 \pm 500$ dyne-second/cm.⁵ There was no further significant change until following the intravenous injection of morphine when

TABLE 1
CHANGES IN CARDIAC INDEX, HEART RATE, STROKE VOLUME, MEAN ARTERIAL PRESSURE AT VARYING CONCENTRATIONS OF CYCLOPROPANE FOLLOWING INTRAVENOUS MORPHINE AND ATROPINE

	Control	Anesthesia Stage		Post-Morphine	Post-Atropine
		III ₁₋₂	III ₃₋₄		
CO ₂ (volumes per cent)		40.6	45.2	45.9	48.4
O ₂ (volumes per cent)		18.2	17.9	18.1	18.2
C ₃ H ₈ (mg.)		16.2	21.0	17.8	16.5
Number of trials	5	10	5	10	10
Cardiac index (l./minute/m ² .)	$2.82 \pm .16$	$2.41 \pm .10$	$1.99 \pm .15$	$1.28 \pm .15$	$2.43 \pm .18$
Heart rate (beats/minute)	103 ± 4	118 ± 10	100 ± 17	56 ± 7	140 ± 4
Stroke volume index (cc./m ² .)	27.3 ± 1.3	21.2 ± 1.5	21.2 ± 3.0	23.2 ± 1.4	17.6 ± 1.6
Number with measurements	3	9	4	8	10
Blood pressure (mm. Hg)	193/98	178/101	158/89	166/74	160/88
Mean pressure (mm. Hg)	146 ± 8	140 ± 4	123 ± 7	120 ± 7	124 ± 3
Total peripheral resistance (dyne-second/cm ⁵ .)	$7,100 \pm 400$	$7,500 \pm 500$	$7,800 \pm 800$	$13,200 \pm 2,000$	$6,900 \pm 700$

(Mean \pm S.E.).

TABLE 2

CHANGES IN THE CARDIAC INDEX, HEART RATE, STROKE VOLUME, MEAN ARTERIAL PRESSURE AND TOTAL PERIPHERAL RESISTANCE IN THE ANIMAL GIVEN MORPHINE, 0.3 MG. PER KILOGRAM INTRAMUSCULARLY, 30 MINUTES BEFORE INDUCTION WITH CYCLOPROPANE AND LEVALLORFAN GIVEN AFTER THE STEADY STATE HAD BEEN REACHED WITH CYCLOPROPANE

Anesthesia Stage	III ₁₋₂	Post-Levallorfan III ₂	Post-Levallorfan III ₃
CO ₂ (volumes per cent)	56.5	42.2	43.3
O ₂ (volumes per cent)	17.5	18.8	21.3
C ₃ H ₆ (mg.)	16.1	18.1	21.1
Cardiac index (l./minute/m ² .)	1.37 ± .41	2.38 ± .31	2.05 ± .44
Heart rate (beats/minute)	54 ± 3	149 ± 15	152 ± 5
Stroke volume index (cc./m ² .)	25.2 ± 3.1	16.2 ± 2.0	13.7 ± 3.3
Blood pressure (mm. Hg)	183/80	177/93	190/107
Mean pressure (mm. Hg)	132 ± 17	135 ± 14	148 ± 4
Total peripheral resistance (dyne-second/cm. ⁵)	13,800 ± 2,100	8,200 ± 1,600	11,300 ± 3,000

(Mean ± S.E.).

there was a marked increase in the peripheral resistance to $13,200 \pm 2,000$ dyne-second/cm.⁵ 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 levallorphan 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 Possati¹⁶ and co-workers. The decreased cardiac index which we found

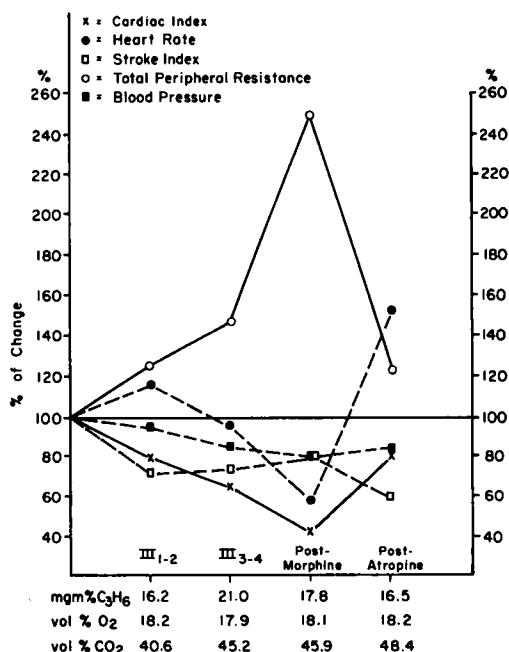


FIG. 1. Percentage changes in heart rate, cardiac index, stroke index and peripheral resistance in dogs anesthetized with cyclopropane and given morphine and then atropine intravenously.

with increasing concentrations of cyclopropane are similar to those reported by other investigators.⁶⁻¹⁰ Prime and Gray⁴ and Thompson and co-workers⁹ and Shackman¹⁷ 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 Baxter¹ 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-workers¹¹ 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_{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 Li⁸ and by Thompson, Patrick and Wood⁹ that the changes in the total peripheral resistance and the pulse rate with cyclopropane are similar to those produced with norepinephrine infusion. Price and associates¹⁸ 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,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,²⁰ Bodo, CoTui and Benaglia,²¹ Houssay and Molinelli.²² The effect of atropine alone in increasing the cardiac index has been shown by McMichael and Sharpy-Schafer²³ 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 Elder²⁴ reported that n-allylnormorphine counteracted the respiratory and vascular depression of morphine.

Also, Smith, Lehman and Gilliafan²⁵ stated that dogs having n-allylnormorphine 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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SPINAL FLUID CIRCULATION Anesthetized 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 received picrotoxin sufficient to produce convulsions 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 convulsions. 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.: Movement of a Dye in the Spinal Subarachnoid 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 concealed 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 paraparesis 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 ameliorated the situation. Clearly, the use in patients of 1 per cent aqueous methylene blue intrathecally is to be interdicted. (*Evans, J. P., and Keegan, H. R.: Danger in Use of Intrathecal Methylene Blue, J. A. M. A.* **174**: 856 (Oct. 15) 1960.)