Effects of Cyclopropane on the Sympathetic Nervous System and on Neural Regulation of Circulation in the Cat

Atsuo F. Fukunaga, M.D.,* and Robert M. Epstein, M.D.†

The effects of cyclopropane on central sympathetic nerve outflow were studied in the cat. Sympathetic nerve activity was measured by recording compound nerve action potentials from the preganglionic splanchnic nerve in normal, decerebrated and baroreceptor-denervated animals. In cats with intact baroreceptors under chloralose anesthesia, the changes in sympathetic discharge, arterial pressure, and heart rate were dependent on cyclopropane dose as follows: During light and moderate cyclopropane anesthesia (10 and 20 per cent) arterial pressure remained essentially unchanged while sympathetic discharge (−17.3 per cent) and heart rate (−8.5 per cent) were both significantly depressed ($P < 0.05$). As the anesthesia was deepened with 40 per cent cyclopropane, arterial pressure fell (−21.0 per cent, $P < 0.05$), but nerve discharge and heart rate returned to control ranges. After denervation of the carotid sinus and aortic baroreceptors in conjunction with the vagus nerves, sympathetic nerve activity, arterial pressure and heart rate were each depressed by cyclopropane in proportion to its inspired concentration. Decerebration alone caused no important change in the pattern of response to cyclopropane in either chloralose-anesthetized or non-anesthetized preparations with intact baroreceptors. Thus, we conclude that barostatic reflex mechanisms are responsible for sustaining the circulation during cyclopropane anesthesia, but that the direct action of cyclopropane on the central vasopressor system is to depress. (Key words: Anesthetics, gases: cyclopropane; Sympathetic nervous system: cyclopropane; Receptors, Presso.: cyclopropane; Blood pressure: cyclopropane; Brain, vasomotor center: cyclopropane.)

Cyclopropane anesthesia in man and experimental animals is known to produce well-maintained or increased blood pressure, increase in cardiac output, positive inotropic actions on the myocardium, and splanchnic and peripheral vasoconstriction. These effects have been attributed to actions on the central sympathetic nervous system.1–2 Price et al.3 have proposed that cyclopropane causes sympathetic excitation by direct effects on the medullary vasomotor neurons. This conclusion was based on the response to electrical stimulation of the brainstem in dogs4 and on measurements of the cervical sympathetic nerve action potentials in the cat.4 In their interpretation, cyclopropane in low concentrations selectively depresses the activity of the medullary vasomotor-inhibitory neurons, while in higher concentrations it directly stimulates the medullary excitatory pressor neurons. Contrary conclusions have been reached in the studies of Markee, Wang, and Wang,5 Bartelstone, Katz, and Ngai,6 and Ngai and Bolme.7 These authors found that in the dog cyclopropane depresses the medullary excitatory mechanisms more than the inhibitory mechanism.

In the present study, we have examined these opposing conclusions concerning the mechanisms of action of cyclopropane on the neural regulation of circulation. Sympathetic activity was measured directly, by continuous recording of the compound nerve action potential from the preganglionic greater splanchnic nerve in the cat.
Material and Methods

Twenty-five adult cats, weighing 2.3–4.7 kg, were studied. Each animal was initially anesthetized with halothane in oxygen delivered into a small animal cage. A tracheotomy was performed, both femoral arteries were cannulated for continuous monitoring of arterial pressure and for arterial blood sampling, and a femoral vein was cannulated for administration of drugs. In 13 cats, chloralose, 40 mg/kg, was injected intravenously. The remaining 12 were not given chloralose but were decerebrated at the midcollicular level. Administration of halothane was then discontinued in all animals, and they were ventilated with 100 per cent oxygen.

The head was placed in a stereotaxic frame and kept in its normal position throughout the experiment. Intermittent positive-pressure ventilation was instituted by means of a Frumin nonrebreathing valve and a modified Frumin-Lee respirator with pediatric bellows which allowed ventilation at a constant pressure. In order to help maintain stable alveolar ventilation, 1 ml of end-tidal gas was sampled from the trachea at each breath by a time-phased sampling pump actuated by the respirator. The sample was passed through a Beckman LB-1 infrared CO₂ analyzer and the percentage of CO₂ was displayed on a polygraph (Offner Dynograph System-In-Vengineering). The rate and tidal volume were further adjusted to maintain PaCO₂ at 30–35 torr as measured with a CO₂ electrode. Arterial blood pressure was measured with a Statham strain gauge transducer, P23De. Mean arterial blood pressure was obtained by electrical damping. Heart rate was recorded using a cardiotachometer coupler triggered by the arterial pulse. The electrocardiogram was recorded from the forelimbs of the cat (lead I). These were all displayed on the polygraph.

Cyclopropane in oxygen was delivered through the nonrebreathing valve using a total flow rate of 2.0–3.0 l/min. End-expired cyclopropane concentration was measured with gas chromatography. The inspiratory oxygen concentration of the gas mixture was monitored with a Beckman Pauling oxygen analyzer, Model D. Room temperature was kept at about 27°C and esophageal temperature was maintained at 36–38°C with the aid of an electric heating pad placed under the animal's body. To prevent movement during the recording of neural activity, small doses of muscle relaxant were given. The 13 cats initially anesthetized with chloralose received 0.1–0.2 mg of pancuronium bromide (Pavulon, Organon, Inc.). The other 12, which were decerebrate, were given 20 mg of gallamine triethiodide intravenously as needed.

The details of the techniques of decerebration, splanchic nerve dissection, and nerve recording have been described.* Briefly, surgical decerebration during hyptensive halothane anesthesia was done at a midcollicular level. Bleeding was always minimal with this technique. The carotid arteries were neither tied nor clamped. For denervation of the baroreceptors, the carotid sinus nerves and the aortic baroreceptor nerves and cervical sympathetic nerves in conjunction with the vagi were severed at a high level in the neck.

The splanchic nerve was located at the left verteobocostal corner retroperitoneally. The left greater splanchic nerve was selected exclusively and cut at its entrance to the celiac ganglion. It was desheathed, immersed in a pool of mineral oil, and covered with cotton. The nerve action potential was recorded from a multimeter made of bipolar platinum wire electrodes (diameter: 22 gauge, interelectrode distance: 2 mm) connected to a Model P15 Grass preamplifier set to a band width of 100–3,000 Hz. The output signals were connected to an oscilloscope and an ultraviolet writing oscillograph (Model 1706, Honeywell) and were stored on magnetic tape along with blood pressure and EKG data. The compound nerve action potentials were rectified and averaged (smoothed) with an electromyograph integrating circuit.

To obtain a quantitative index of the magnitude of neural activity, the smoothed neural signal was integrated using a self-resetting integrator designed by A. S. J. Lee. Each nerve was tested for responsiveness by giving 5 μg of epinephrine or histamine intravenously. At the end of the experiment, a few drops of procaine hydrochloride (1 per cent) were placed on the nerve central to the

† Chloralose was dissolved in a 10 per cent solution of polyethylene glycol 400.
SYMPATHETIC NERVE ACTIVITY DURING CYCLOPROPANE

TABLE 1. Arterial Blood Gases, pH and Esophageal Temperatures*

<table>
<thead>
<tr>
<th></th>
<th>Control (100 Per Cent O₂)</th>
<th>Cyclopropane (10-20 Per Cent)</th>
<th>Cyclopropane (40-50 Per Cent)</th>
<th>Recovery (100 Per Cent O₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCO₂ (torr)</td>
<td>30 ± 1.0 (35)</td>
<td>29 ± 1.3 (30)</td>
<td>30 ± 3.6 (8)</td>
<td>32 ± 1.6 (26)</td>
</tr>
<tr>
<td>PO₂ (torr)</td>
<td>534 ± 9.2 (35)</td>
<td>442 ± 9.3 (29)</td>
<td>258 ± 16.4 (8)</td>
<td>520 ± 12.2 (28)</td>
</tr>
<tr>
<td>pH</td>
<td>7.33 ± 0.01 (35)</td>
<td>7.35 ± 0.01 (30)</td>
<td>7.33 ± 0.04 (8)</td>
<td>7.31 ± 0.01 (30)</td>
</tr>
<tr>
<td>Temperature (C)</td>
<td>37.5 ± 0.3 (35)</td>
<td>37.0 ± 0.2 (30)</td>
<td>37.1 ± 0.3 (8)</td>
<td>37.0 ± 0.2 (31)</td>
</tr>
</tbody>
</table>

* ( ): Number of samples.

Electrodes. The residual signal level was taken to be the zero neural activity and the integrator baseline was set to this level, so that all recorded neural activity above the baseline was counted. Audio monitoring of the nerve discharge was used throughout the experiment.

All measurements were taken from original recordings, or in the case of the resetting integrator, from the data recorded on magnetic tape replayed at the original speed. For display purposes only, the figures presented here are taken from the taped data replayed at 1/8 or 1/16th of the original speed and recorded on a Brush 220 ink recorder. This change of speed permits reproduction of the original high-frequency signals on the ink recorder.

Experimental Protocol

Simultaneous recordings of neural activity, arterial pressure, and heart rate were made in four experimental preparations during inhalation of cyclopropane. Six cats were studied with chloralose basal anesthesia alone (normal animals). Four of these six were afterwards decerebrated (anesthetized-decerebrate animals). In the remaining two and an additional seven, the baroreceptor nerves were denervated (debuffered animals). The fourth group comprised 12 cats studied with no basal anesthetic after removal of the forebrain during halothane anesthesia (nonanesthetized decerebrate animals).

The measurements were started after the cat’s condition had stabilized following each surgical procedure and more than two hours after the discontinuation of halothane. All animals were ventilated with 100 per cent oxygen except during those times when cyclopropane was added to the inspired gas. Directly after control values had been obtained, the animals were exposed to cyclopropane for 15 to 55 minutes and recordings made at intervals of 5 minutes. Concentration was increased stepwise to 10, 20 and 40 per cent at intervals of 15 minutes, and in four of the debuffered animals, was increased finally to 50 per cent. In eight of the nonanesthetized decerebrate cats, 10 or 20 per cent cyclopropane in oxygen was given intermittently for 15 minutes at a time in either single or repeated exposures. Recovery values were measured about 30 minutes after discontinuation of cyclopropane.

In the debuffered preparation with chloralose basal anesthesia (nine cats), when the buffer nerves were removed, arterial pressure rose, often exceeding 200 torr systolic. Therefore, the start of the study was delayed until after arterial pressure returned to the level before denervation. With marked persistent hypertension in five of the nine cats, arterial pressure was controlled by partial exsanguination through the femoral arterial catheter. The blood withdrawn averaged 33 ± 12 ml.

All data were tested with Student’s t test for paired data. P < 5 per cent was considered significant. The data are expressed as means ± SE.

Results

Table 1 shows certain systemic effects of the experiment in all cats taken together. Individual changes were small in any one animal. End-tidal CO₂ concentrations were maintained in the range of 4.0-5.0 per cent. Measurements in arterial blood revealed no significant change in PaCO₂ or pH. Changes in PaO₂ were consistent with the reduction of FiO₂ during administration of cyclopropane,
Fig. 1. Effects of cyclopropane on preganglionic splanchnic nerve discharge and arterial blood pressure in a single cat. Normal animal (intact baroreceptors) under chloralose basal anesthesia (40 mg/kg). Spl. N: splanchnic nerve action potential (upper trace); Sm. Spl. N: smoothed splanchnic nerve activity and zero line after procaine (middle trace); B.P.: arterial blood pressure (lower trace). The number on the right-hand side of each panel gives the integrated value for splanchnic nerve activity over one minute's recording. Recordings: control with 100 per cent oxygen, exposure to cyclopropane in each concentration for 10 minutes, after 30 minutes recovery with 100 per cent oxygen and after application of procaine. Smoothed value is in arbitrary units. Note that sympathetic discharge increased with the higher concentrations of cyclopropane when arterial hypotension and cardiac arrhythmias developed.

and in no case was PaO₂ less than 150 torr. Body temperatures remained approximately 37°C.

The effects of inhalation of cyclopropane on the sympathetic nerve action potentials recorded from the preganglionic splanchnic nerve differed strikingly between the groups of cats with intact and with denervated baroreceptors. In those with intact baroreceptors, the changes were variable and depended upon the inspired concentration of cyclopropane. The arterial pressure and cardiac action likewise showed variable changes, including both hypotension and mild hypertension, and both narrowing and widening of pulse pressure, and accompanying cardiac arrhythmias. On the other hand, in cats whose baroreceptor and vagus nerves were sectioned, cyclopropane caused consistent depression of splanchnic nerve activity, blood pressure, and heart rate. Typical changes in neural activity and arterial blood pressure in single animals are presented in figures 1 and 2. Figures 3 to 6 show the sequential changes in neural activity, blood pressure, and heart rate during the entire course of the experiments. The individual points shown were pooled in constructing the summary of results, table 2.

Anesthetized Preparations

Intact cats (six animals) (table 2, fig. 3). Cyclopropane, 10 per cent, caused slight elevations in mean arterial pressure when measured after 5, 10 and 15 minutes of exposure. There were, however, significant depressions of splanchnic nerve activity (−17 per cent, P < 0.05) and heart rate (−4 per cent, P < 0.05). On increasing the inspiratory cyclopropane concentration to 20 per cent, arterial...
pressure fell to slightly below control, and splanchnic nerve activity attained its lowest level at 5 minutes (–20 per cent, P < 0.05), but after 10 and 15 minutes of exposure the neural activity showed a slight tendency to increase, while heart rate was further decreased and remained at its lowest level.

When the anesthesia was deepened with 40 per cent cyclopropane, blood pressure dropped sharply (–21 per cent, P < 0.05). In contrast, splanchnic nerve activity and heart rate began to increase, and in three of six cats neural activity exceeded controls (figs. 1 and 3), but the overall increase in splanchnic nerve activity was not significant (P > 0.50). In these animals, the highest concentration of cyclopropane frequently caused cardiac arrhythmias.

Debuffered cats (nine animals) (table 2, fig. 4). Inhalation of 10 per cent cyclopropane caused highly significant reductions in arterial blood pressure (–27 per cent, P < 0.001), splanchnic nerve activity (–20 per cent, P < 0.01) and the heart rate (–4 per cent, P < 0.05). With 20 per cent cyclopropane, changes were even more exaggerated. The decrease in blood pressure was 39 per cent (P < 0.001); splanchnic nerve activity, 32 per cent (P < 0.01); heart rate, 7 per cent (P < 0.01). A further decrease of each developed when 40 per cent cyclopropane was administered; the maximal depressions in splanchnic nerve activity (–45 per cent), arterial pressure (–57 per cent) and heart rate (–17 per cent) were then recorded. Statistically, all these changes were highly significant (P < 0.001).

The 40 per cent concentration of cyclopropane caused arterial hypotension in all nine debuffered cats, and the blood which had been withdrawn previously was replaced in three in order to maintain systolic arterial pressures above 60 torr. In one cat, profound hypotension (40 torr, systolic) developed despite this, and splanchnic nerve activity showed an unusual discharge pattern which may have been caused by ischemia in the central nervous system. The administration of cyclopropane was discontinued in this cat and the data for this concentration were discarded. In
FIG. 3. Responses of splanchnic nerve activity, mean arterial blood pressure and heart rate to cyclopropane in normal cats during chloralose basal anesthesia, baroreceptors intact. ISN (*): integral of smoothed splanchnic nerve activity; MABP (△): mean arterial blood pressure; HR (○): heart rate; n: number of animals. Significance of change from control: * = P < 0.05, ** = P < 0.01, *** = P < 0.001.

FIG. 4. As in figure 3, animals with baroreceptors denervated.

FIG. 5. As in figure 3, decerebrated animals with intact baroreceptors, chloralose basal anesthesia.
four of the five animals whose arterial pressures were maintained without need for infusion of blood, cyclopropane concentration was raised from 40 to 50 per cent for 10 minutes. This caused further depressions of splanchnic nerve activity, arterial blood pressure, and heart rate. Figure 7 illustrates the changes in sympathetic nerve discharge, mean arterial pressure, and heart rate during the entire course of the experiment in a single debuffed cat.

Decerebrate cats (four animals) (table 2, fig. 5). The decerebrate cats under basal anesthesia with chloralose and with baroreceptor nerves intact showed patterns of response similar to those observed in animals with normal brains, except that the reductions in the variables measured during administration of cyclopropane were intensified (fig. 5). Changes with 10 and 20 per cent cyclopropane were: arterial pressure -11 and -15 per cent; splanchnic nerve activity -21 and -20 per cent; heart rate -10 and -14 per cent. When 40 per cent cyclopropane was inhaled, the arterial pressure dropped further, to its lowest level. The neural activity and heart rate began to increase when arterial pressure fell markedly, but these increased values never exceeded controls and were not significant.

NON-ANESTHETIZED PREPARATION

Decerebrate cats (12 animals) (table 2, fig. 6). Since the responses to different concentrations of cyclopropane were similar in all 12 animals regardless of the time sequence of administration, the collected data were analyzed together for each concentration of cyclopropane. The changes were variable from one experiment to another; none proved statistically significant. In each individual preparation, however, changes in neural activity and arterial pressure showed good reciprocal correlation. At no time did increases in arterial pressure seem related to enhanced sympathetic nerve discharge.

CHANGES DURING RECOVERY

The recovery values tabulated were measured after administration of cyclopropane had been discontinued for 30.7 ± 1.5 minutes. Although administration lasted as long as

75-85 minutes, splanchnic nerve activity, arterial pressure, and heart rate recovered satisfactorily near to controls (figs. 3-7).

In the cats with intact baroreceptors, there were sharp overshoots of arterial pressures 2-3 minutes after discontinuation of cyclopropane, but neural activity tended to recover more gradually. In the debuffed animals, the usual observation was that pressures fell briefly, did not rise as fast, but in the end transiently exceeded controls. Neural activity increased almost immediately and then fluctuated in parallel with arterial pressure (figs. 4 and 7).

CARDIAC ARRHYTHMIAS

Irregular cardiac rhythms occurred frequently during inhalation of cyclopropane provided that the baroreceptor nerves were intact. During chloralose basal anesthesia, four of six normal cats (67 per cent) developed ventricular extrastoles. Nine of 16 decerebrate cats (56 per cent) developed arrhythmias. In contrast, none of the nine animals whose baroreceptor and vagus nerves were transected showed cardiac irregularities, although at times heart rates showed and QRS complexes were moderately prolonged. These changes were observed only when severe hypotension had been induced.
<table>
<thead>
<tr>
<th>Table 2. Effects of Cyclopropane</th>
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<tr>
<td><strong>Inspiratory Cyclopropane Concentration (Vol. Per Cent)</strong></td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td><strong>Intact animals, chloralose anesthesia</strong></td>
</tr>
<tr>
<td>Control*</td>
</tr>
<tr>
<td>10 per cent</td>
</tr>
<tr>
<td>20 per cent</td>
</tr>
<tr>
<td>40 per cent</td>
</tr>
<tr>
<td>Recovery</td>
</tr>
<tr>
<td><strong>Debuffered animals, chloralose anesthesia</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>10 per cent</td>
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<tr>
<td>20 per cent</td>
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<tr>
<td>40 per cent</td>
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<tr>
<td>50 per cent</td>
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<tr>
<td><strong>Decerebrate animals, chloralose anesthesia</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>10 per cent</td>
</tr>
<tr>
<td>20 per cent</td>
</tr>
<tr>
<td>40 per cent</td>
</tr>
<tr>
<td>Recovery</td>
</tr>
<tr>
<td><strong>Decerebrate animals, no chloralose, buffer nerves intact</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>10 per cent</td>
</tr>
<tr>
<td>Recovery</td>
</tr>
<tr>
<td><strong>Control</strong></td>
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<td>20 per cent</td>
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<td>Recovery</td>
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<tr>
<td><strong>Control</strong></td>
</tr>
<tr>
<td>40 per cent</td>
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<tr>
<td>Recovery</td>
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* 100 per cent oxygen.
Significance of change from control:
† P < 0.05.
‡ P < 0.01.
§ P < 0.001.

Discussion

The efferent preganglionic splanchnic nerve action potential was measured in these studies as an indicator of the activity of the central sympathetic nervous system. We assume that the activity of the central sympathetic nervous system will be manifested by correlated changes in peripheral sympathetic nerve discharge and cardiovascular activities. Significant variations in sympathetic outflow, however, may be induced reflexly by several mechanisms modifying the activity of the central vasomotor center. Even a transient change in arterial pressure will greatly influence central vasomotor neurons through the baroreflex system. The anesthetic used may alter the sensitivity of the baroreceptors and may exert direct action upon medullary vasomotor neurons as well. Finally, suprapontine structures such as preoptic and hypothalamic neurons may modify total sympathetic outflow.

Removal of the forebrain by transection of
the midbrain (deceretration) offers a preparation which avoids the use of basal anesthetics and the effects of suprapontine sympathetic structures. It is generally believed that decerebration at the midcollicular level does not impair the basic reflex mechanisms affecting the circulation, although it unquestionably removes modulator mechanisms from the more rostral sites. Interruption of the baroreceptor system uncouples efferent nerve activity from reflex responses to arterial pressure. Given adequate perfusion of the brainstem, the observed sympathetic nerve discharge can be assumed to reflect intrinsic and drug-induced activity of central origin, most likely that of excitatory vasomotor neurons.

The effects of cyclopropane at various concentrations from light to deep were tested in the intact, decerebrate, and debuffered cats. In animals with intact baroreceptors responses to cyclopropane were very variable, depending upon inspired concentration of cyclopropane and changes in arterial pressure. Careful analysis of the data shows that: 1) there was always a reciprocal correlation between changes in sympathetic nerve activity and arterial pressure, and 2) changes in arterial pressure always preceded changes in neural activity. Hence, the observations in these animals strongly suggest that any increases in sympathetic nerve discharge arise in the barostatic reflex system in response to a vasodepressor action of cyclopropane.

This view was further substantiated by the experiments with the cats with denervated baroreceptors. In these, arterial pressures were consistently depressed, initial hypotension was more pronounced, and there was no rebound rise. Neural activity progressively declined, and the higher the concentration of cyclopropane administered, the more profound the depression, within the limits of effective perfusion pressure. Decreases in arterial pressure and sympathetic nerve activity were always proportional to the concentration of cyclopropane administered.

Our studies appear to be clear of technical concerns. Particularly, we find our results to be reproducible. The preparations are stable. They showed excellent recovery after exposures to cyclopropane lasting as long as 75 or 85 minutes, so there was no need to "correct" baseline values to analyze our results. We infer that cyclopropane depresses central sympathetic activity. Our findings contradict a prevailing belief that cyclopropane causes sympathetic activation by direct action on central sympathetic vasomotor neurons.

Many studies in which sympathomimetic effects have been demonstrated during cyclopropane anesthesia have been reported. These effects have included elevated arterial pressure, increased plasma catecholamine...
levels, cardiac arrhythmias, well-maintained cardiac contractility, and regional vasoconstriction. Millar and Bischof studied the rabbit and later, Price et al. studied the cat. Millar reported that inhalation of cyclopropane increased neural activity in the cervical as well as in the splanchnic nerve in the rabbit anesthetized with sodium pentobarbital. The results in the rabbit do not seem representative, since Millar reported that the rabbit’s splanchnic nerve activity showed “atypical” patterns, and that intravenously injected epinephrine, which normally depresses neural activity reflexly, instead increased neural activity by arterial pressure was increased. (Again, in the rabbit, Millar found that halothane, generally acknowledged to depress the central sympathetic system, caused sympathetic excitation.) Caution must be used in applying data from the rabbit to other species.

Price observed increased cervical sympathetic nerve discharge during administration of cyclopropane to the cat. With high concentrations the decreases in arterial pressure and cervical sympathetic nerve discharge following electrical stimulation of the aortic depressor nerve were completely abolished. Price concluded that the increased sympathetic outflow is caused by preferential inhibition of the medullary depressor neurons with low concentrations of cyclopropane, and that the higher concentrations directly stimulate the medullary pressor neurons.

There are several possible factors which may explain the discrepancies between our results and those of previous workers. Of the many possible sympathetic nerves, we chose the greater splanchnic nerve for recording of compound nerve action potentials. Price examined responses to cyclopropane in the cervical sympathetic nerve, assuming that the cervical sympathetic fibers are representative. Some previous evidence supports this view. However, the cervical nerve innervates the head and neck, and its efferent fibers include not only vasomotor fibers but also pupillodilator, secretory (salivary, parotid, and lacrimal glands), and pilomotor fibers. Moreover, its vasomotor fibers respond selectively only to intense homolateral brainstem stimulation, unlike the more diffuse and sensitive responses of the cardioaccelerator fibers, suggesting that they are more selectively involved with local control mechanisms than with generalized sympathetic responses. It is unlikely that the function of this nerve is of primary importance in regulation of systemic as opposed to local circulation, even though fibers selected for study were inhibited by epinephrine-induced pressor effects. Activity in the efferent splanchnic nerve, in contrast, has been generally reported to be closely correlated with systemic cardiovascular responses.

There are significant differences between the techniques used to quantitate neural activity in our study and in those of Price and Millar. We accept as neural traffic all recorded activity of amplitudes greater than that obtained following terminal application of procaine. As is evident in figures 1 and 2, much of the total activity in the nerve is burst-like, but the “background” level of discharge is always greater than the procaine “noise” level. It does not represent noise. This can be demonstrated easily by suppressing the neural output with small intravenous doses of epinephrine, as we do routinely to test neural responsiveness. Selection of strands showing high-voltage spikes above an arbitrary limit which nerve action potentials must exceed to be included, with conversion of these to unit impulses to be counted (the technique of Price and of Millar), risks the possibility of excluding large portions of the total activity, particularly that from smaller fibers, which is continuous although of low level. We believe this technique may have led to differences between the values ascribed to compound nerve action potential activity from the preganglionic nerve trunks in our respective studies.

Another difference between our techniques is in the relaxants chosen to produce quiet preparations. Gallamine has been traditionally selected, and we used it in our first studies, those on the nonanesthetized decerebrate cat. These animals showed the least depression of sympathetic discharge with cyclopropane of our four experimental groups. Gallamine was discontinued in the other experimental groups since it is now believed that it has a sympathomimetic action, at least on the
SYMPATHETIC NERVE ACTIVITY DURING CYCLOPROANE

As the systolic pressure which occurs despite the depression of sympathetic nerve activity in some individual animals with intact baroreceptors during light anesthesia may be explained by a sensitivity change in the receptor sites. Peripheral tissues, such as the aortic strip, nictitating membrane, and Purkinje fibers, show greatly enhanced responses to catecholamines in the presence of cyclopropane. In our cats with intact baroreceptors, transient arterial hypotension invariably occurred initially during the induction of cyclopropane anesthesia; this was then antagonized by sudden and transient "bursts" of sympathetic nerve discharge. The resulting pressure reflects a balance of anesthetic depression of the nervous system, continued reflex activation, and a sensitized adrenergic effector system. In contrast, bursts of nerve discharge were not observed in the absence of baroregulatory compensatory mechanisms and, in turn, cyclopropane did not cause any elevation of arterial pressure in the debuffered animals.

Price and Widdicombe reported that cyclopropane increased the afferent carotid sinus nerve impulses in the dog and the cat. The increased negative feedback from the sensitized baroreceptors would be expected to accentuate the centrally caused tendency to reduced sympathetic nerve discharge. Since this did not occur, sufficient withdrawal of this afferent traffic (by a tendency to reduce arterial blood pressure) to offset this change may be present in the intact animal. Alternatively, there may be changes at the central connections of the reflex arc as well. Since arterial pressure often increased, the latter appears to be a real possibility. An experimental model studied with electrical stimulation of the central cut end of the buffer nerves would help to answer this question.

Observations of heart rate and rhythm, also believed to reflect the activities of the central autonomic nervous system, may offer some additional support for our interpretation of the changes in sympathetic discharge. Induction of cyclopropane anesthesia caused a very high incidence of cardiac arrhythmias, but in this study this occurred only in animals with intact baroreceptors, in which arterial pressure and sympathetic discharge were well maintained. The absence of arrhythmias is in accord
with our finding that sympathetic depression occurred with cyclopropane in baroreceptor-denervated preparations.

We conclude from the results obtained in four experimental models that any increases in sympathetic discharge seen during cyclopropane anesthesia are not caused by a direct action of cyclopropane on the central vasomotor center but are homeostatic reflex responses mediated through the baroreceptor system. The direct action of cyclopropane on the vasopressor-vasodepressor balance of the medullary sympathetic system is depressant.

References


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Circulation

THE STONE HEART A distinctive fatal complication affected the hearts of 13 of 4,732 patients who underwent open-heart surgery at the Texas Heart Institute. During or at the conclusion of cardiopulmonary bypass an unyielding, firm, spastically contracted heart was discovered, which engendered the term “stone heart.” These 13 patients were men, ranging in age from 42 to 73 years, being operated upon for calcific aortic stenosis supplemented, in three instances, by coronary-artery bypass grafts. Prominent among the diagnostic preoperative information were congestive heart failure (11 patients), angina pectoris (8 patients), left ventricular hypertrophy (8 patients), and prior myocardial infarction (4 patients). The patients submitted to preoperative cardiac catheterization showed severe elevations of aortic valve gradients and left ventricular systolic and end-diastolic pressures, and pulmonary hypertension. Post mortem, myocardial hypertrophy was found in all 13 patients; heart weights ranged from 620 to 1,277 g (mean 782 g). Evidence of coronary-artery disease was found in nine patients, three of whom had recently had infarctions. After these observations were made, the technique of cardiopulmonary bypass was modified for patients with identifiably ischemic myocardium, by the addition of hypothermia to 30°C, without coronary-artery perfusion, supplemented by exposure of the heart to cold saline solution until systemic normothermia was restored. The aortic clamp was then released. Subsequently, none of 266 patients undergoing aortic valve replacement has developed the stone heart. More definitive investigation of myocardial metabolism, particularly the relationship between adenosine triphosphate (ATP) deficiency and this syndrome, is suggested. (Wukasch, D.C., and others: “The Stone Heart” Syndrome. Surgery 72:1071–1080, 1972.)

Abstracter’s Comment: This paper credibly and lucidly identifies the predisposing factors of a puzzling fatal complication of open-heart surgery. However, the efficacy of the suggested preventive measures is less convincing because the number on which the conclusion is based (266 patients) is less than the incidence (1:364) among the previous series of 4,732 patients. This complication has been reported subsequently from other centers, despite the use of myocardial hypothermia. The changes described probably arise secondary to excessive ischemia. At present there appears to be no reliable method of treatment. Whether anesthetic or inotropic drugs promote the appearance of the “stone heart” syndrome whenever myocardial ischemia has been produced deserves further study.