Effects of Alpha and Beta Adrenergic Blocking Agents on Cyclopropane-Catecholamine Cardiac Arrhythmias

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Cardiac arrhythmias were produced in the cat by the injection of epinephrine, norepinephrine, ethynorepinephrine or isoproterenol during the inhalation of 25 per cent cyclopropane in oxygen. The injection of dibenamine, an alpha adrenergic blocking agent, produced epinephrine reversal, decreased the pressor response to norepinephrine and increased the depressor response to isoproterenol. Dibenamine did not consistently increase the threshold doses of catecholamines required to produce cardiac arrhythmias. In those instances where the arrhythmia threshold doses of the catecholamines were increased, usually to twice control, this result often was attributable to a modification by dibenamine of the pressor effects of the catecholamines. The beta adrenergic blocking agent pronethalol produced ethynorepinephrine reversal, increased the pressor response to epinephrine and markedly reduced or abolished the depressor response to isoproterenol. The arrhythmia threshold doses of the catecholamines were increased to 8 times those of controls. Large doses of isoproterenol (3 mg./kg.) produced beta adrenergic blockade and increased the arrhythmia threshold doses of the catecholamines to 4 times those of controls. The results suggest that cyclopropane-catecholamine arrhythmias are blocked by specific beta adrenergic blockade and that myocardial ectopic excitation may be attributable to the beta adrenergic receptors.

It has been convenient to attribute some of the effects of catecholamines to alpha or beta adrenergic receptor stimulation. The demonstration that the alpha adrenergic blocking agent dibenamine prevented catecholamine-induced cardiac arrhythmias appeared to support the classification of myocardial ectopic excitation as an alpha adrenergic effect. It has been questioned, however, whether the antiarrhythmic action of dibenamine was attributable to the effect of lowering blood pressure or the quinidine-like action of dibenamine rather than to a specific alpha adrenergic blockade. The demonstration that the beta adrenergic blocking agents dichloroisoproterenol (DCI) and pronethalol prevent catecholamine-induced arrhythmias suggested that cardiac arrhythmias might be attributable to beta adrenergic stimulation. The present study was undertaken to compare and contrast the effects of dibenamine and pronethalol on cyclopropane-catecholamine cardiac arrhythmias in the cat.

Methods

Forty cats weighing 2–4 kg. were studied. The animal was placed in a clear plastic box to which 25 per cent cyclopropane in oxygen was delivered from a Ventirol anesthesia machine. When anesthesia was established the animal was removed from the box, and a tracheotomy performed rapidly. Cyclopropane and oxygen were then given via a nonrebreathing system (Sierra nonrebreathing valve 28–560) and the lungs ventilated with a Frumin respirator (pediatric bellows). The femoral artery and femoral vein were cannulated. Femoral arterial pressure was measured with a Statham transducer. In some animals the common carotid arterial pressure was measured. Lead 2 of the electrocardiogram and arterial pressure were recorded on a Grass polygraph at a paper speed of 2.5 or 25 mm./second. In order to insure the adequacy of ventilation, arterial blood samples were drawn at appropriate intervals for analysis of pH and P(02). (Astrup AME-1). Ventilation was adjusted so that the pH and P(02) were in the range of 7.30–7.35 units and 30–35 mm. of mercury, respectively. All injections were made into the femoral vein. A heating pad...
was used to maintain the rectal temperature within one degree Centigrade of control.

The following drugs were used: epinephrine HCl (E), norepinephrine bitartrate (NE), isoproterenol HCl (ISOP), ethylisopropinephrine HCl (ENE), dibenamine, and pronethalol (also known as nethalide, alderlin, Ay-6204). The doses are expressed in terms of the salts except for NE which is expressed in terms of the base. The catecholamines were appropriately diluted with saline so that the volume injected was 0.5–1 ml. A 1 per cent solution of pronethalol and 5 per cent solution of dibenamine were diluted with saline to 10 ml so as to permit a slow rate of infusion.

The threshold dose of catecholamine required to produce cardiac arrhythmias during 25 per cent cyclopropane in oxygen inhalation was determined in the following manner: 0.125 μg./kg. of E was injected and the response determined. If an arrhythmia (at least 10 ventricular ectopic beats) was not observed, the dose of E was doubled until an arrhythmia was produced. The interval between injections (a minimum of ten minutes) was determined by the time required for the blood pressure and heart rate to return to the control level. The arrhythmia thresholds for NE, ISOP, and ENE were determined in a similar fashion. The initial dose of NE and of ISOP was 0.125 μg./kg., while the initial dose of ENE was 6.25 μg./kg. The duration of arrhythmias with these agents varied from 20–120 seconds. After the injection of 10 ml of saline, the arrhythmia threshold was reetermined by injecting one-half the threshold dose and then doubling the dose until an arrhythmia was produced. In the rare situation where the threshold decreased, a new threshold was determined by starting with a subarrhythmic dose. In 12 animals the arrhythmia thresholds for E, NE, ISOP and ENE were compared, while in 20 animals only the first three agents were compared. Two or three of the four agents were compared in eight animals. In 10 of these 40 animals a ligature was placed around the descending aorta so that the blood pressure could be raised by constricting the aorta.

Once the arrhythmia threshold had been established, dibenamine (5, 10 or 20 mg./kg.) was given and the arrhythmia threshold redetermined. In some animals the total dose of dibenamine was given in one infusion, while in others the arrhythmia threshold was determined after 5, 10 and 20 mg./kg. The arrhythmia threshold before and after pronethalol (2.5, 5, 10 mg./kg.) was determined in a similar fashion.

Results (Table 1)

Reproducibility of Thresholds. In five animals the arrhythmia thresholds for E, NE, ENE, ISOP were determined three times. The threshold dose was doubled in four determinations, halved in two determinations and unchanged in 54 determinations. In addition, in each animal, before determining the effects of dibenamine or pronethalol the arrhythmia threshold was determined before and after the injection of 10 ml of saline. The threshold reproducibility was similar to that seen in the five animals described above. Where a change in threshold was seen, a consistent threshold was established prior to determining the effects of dibenamine or pronethalol. Consistent thresholds could not be established in five animals, which were therefore not studied.

Effects of E, NE, ENE, ISOP. The mean heart rate and blood pressure during cyclopropane prior to the injection of catecholamines were 98 (Range of 70–140) and 142 89 (Range of 105–200 60–140). The smaller doses of E (0.125–0.5 μg./kg.) produced brief (30–90 seconds) variable changes in blood pressure and heart rate. The blood pressure most often increased 10–25 per cent, but sometimes decreased 10–25 per cent, increased and then decreased, or was unchanged. The magnitudes of increase in systolic and in diastolic pressure were usually similar, however when the mean arterial pressure fell, diastolic pressure usually decreased more than systolic pressure. The heart rate was unchanged or increased 10–30 per cent. Larger doses of E (1–4 μg./kg.) consistently increased the blood pressure and heart rate 15–40 per cent for 1–2 minutes. Cardiac arrhythmias were produced by E in 37 of 38 animals. The mean arrhythmic threshold dose was 0.9 μg. kg. (range of 0.125–4 μg. kg.). Although cardiac arrhythmias were most often associated with a rise in blood pressure, they were also seen with no change or a fall in blood pressure.
Table 1. Effects of Dibenamine, Pronethalol and Isoproterenol on Cyclopropane-Catecholamine Arrhythmia Thresholds

<table>
<thead>
<tr>
<th>Control</th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
<th>Isoproterenol</th>
<th>Ethynovpinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia threshold dose (µg/kg)</td>
<td>0.9</td>
<td>0.75</td>
<td>1.2</td>
<td>41</td>
</tr>
<tr>
<td>Mean</td>
<td>0.125–4</td>
<td>0.125–4</td>
<td>0.125–4</td>
<td>12.5–100</td>
</tr>
<tr>
<td>Range</td>
<td>35 of 35</td>
<td>28 of 36</td>
<td>14 of 18</td>
<td></td>
</tr>
<tr>
<td>Frequency of arrhythmia</td>
<td>37 of 38</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dibenamine (5–20 mg./kg.)
- Threshold not increased | 9 | 11 | 12 | 6 |
- Threshold Increased 2 X | 9 | 4 | 2 | 3 |
- Threshold Increased 4 X | 2 | 1 | 1 | 0 |

Pronethalol (2.5–10 mg./kg.)
- Threshold not increased | 1 | 1 | 0 | 0 |
- Threshold Increased 4 X | 2 | 2 | 1 | 0 |
- Threshold Increased 8 X | 6 | 6 | 4 | 3 |
- Threshold Increased 16 X | 1 | 1 | 2 | 0 |

Isoproterenol (3 mg./kg.)
- Threshold not increased | 1 | 1 | 1 | 0 |
- Threshold Increased 4 X | 4 | 4 | 3 | 2 |

NE (0.125–0.5 µg./kg.) usually produced a 10–30 per cent increase in systolic and diastolic pressure for 30–90 seconds. Larger doses (1–4 µg./kg.) increased systolic and diastolic pressure 15–60 per cent for 1–3 minutes. The heart rate was unchanged or decreased during the increase in blood pressure. Cardiac arrhythmias were produced in all 35 animals studied. The mean arrhythmia threshold dose was 0.75 µg./kg. (range of 0.125–4 µg./kg.).

ISOP (0.125–4 µg./kg.) usually decreased systolic pressure by 10–25 per cent and diastolic pressure by 15–50 per cent. The decrease in pressure varied from 0.5 to 3 minutes. Upon recovery the blood pressure frequently rose to a level 10–20 per cent higher than control. The heart rate usually increased 20–40 per cent. Cardiac arrhythmias were seen in 28 of 36 animals. The dose required to decrease blood pressure and increase heart rate was invariably less than that required to produce cardiac arrhythmias. The mean arrhythmia threshold dose was 1.2 µg./kg. (range of 0.125–4 µg./kg.). It was noted in eight animals that ISOP initially decreased blood pressure, increased heart rate, but did not produce arrhythmias. However, as the blood pressure recovered to or above control, arrhythmias were seen. If the dose of ISOP was increased, arrhythmias could now be produced during the fall in blood pressure. At the nadir of the fall, a normal sinus rhythm returned but cardiac arrhythmias were again seen as the blood pressure rose. A further increase in the dose of ISOP produced a merging of the early and late arrhythmias. In five animals a sub-arrhythmic threshold dose of ISOP which produced a fall in blood pressure was given. When the same dose of ISOP was repeated and the aorta constricted 3 seconds after the injection, the blood pressure either did not fall or rose and arrhythmias were seen in four of the five animals. Although the arrhythmia could be maintained for more than 60 seconds, releasing the clamp after 20–30 seconds produced an immediate fall in blood pressure and restoration of a normal sinus rhythm. Constricting the aorta without injecting ISOP increased the blood pressure 20–33 per cent but did not produce arrhythmias in any of the five animals.

ENE (6.25–100 µg./kg.) usually produced a decrease in the mean arterial blood pressure. This was brought about by a 20–50 per cent decrease in diastolic pressure and a smaller decrease (10–20 per cent), no change, or 5–10
per cent increase in systolic pressure. Upon recovery the systolic and diastolic pressure frequently rose to a level of 10–20 per cent higher than control. The heart rate usually increased 20–40 per cent. Arrhythmias were seen in 14 of 18 cats. The mean arrhythmic threshold dose was 41 µg./kg. (range of 12.5 to 100 µg./kg.). As with ISOP, ENE in some animals initially produced a normal sinus rhythm and decrease in mean arterial pressure, which was followed by a late rise in blood pressure and arrhythmias. Increasing the dose of ENE produced arrhythmias as the mean arterial pressure fell.

**Effects of Dibenamine.** The slow intravenous infusion of 5–20 mg./kg. of dimenamine at a rate of 0.5–1 mg./kg./minute produced no change or a 10–25 per cent decrease in blood pressure. No injections were made for at least 30 minutes after the end of the infusion in order to permit an alpha adrenergic blockade to develop and to permit the blood pressure to stabilize. In two animals the blood pressure fell precipitously during the infusion of dibenamine and the animals expired.

Dibenamine (5–20 mg./kg.) produced E reversal (a fall in blood pressure rather than an increase after the injection of E), decreased the pressor response to NE, increased the depressor response to ENE and had little effect on the depressor response to ISOP. In nine animals dibenamine had no effect on the arrhythmia thresholds for NE, ISOP, ENE or E (despite E reversal) (fig. 1). However, in 11 animals the arrhythmia threshold dose of E increased to twice that of control (nine animals) and four times control (two animals). In three of four animals the threshold was returned to the control level by constricting the aorta and preventing E reversal. In these 11 animals in which the arrhythmia threshold with E was increased, the following changes in ar-
rhythmia threshold with NE, ISOP and ENE were observed: (1) NE—unchanged in 4, increased in 5; (2) ISOP—unchanged in 6, increased in 3; (3) ENE—unchanged in 2, increased in 3. In the 11 instances in which the arrhythmia threshold for NE, ENE and ISOP increased, the increase was to twice control in nine experiments and four times control in two experiments. The different effects of dibenamine on the arrhythmia thresholds for E and ISOP in the same animal may be seen in figure 2. Although dibenamine produced E reversal and raised the arrhythmia threshold for E, the arrhythmia threshold for ISOP was unchanged.

In the experiments with ISOP in which the control blood pressure and heart rate responses to ISOP before and after dibenamine were similar, the threshold was increased (to twice control) in three experiments (fig. 3) and was unchanged in eight (fig. 2, C and D).

Effects of Pronethalol. The injection of 2.5–10 mg./kg. of pronethalol (rate of 1 mg./kg./minute) produced no change or a 10–20 per cent decrease in blood pressure and a 20–33 per cent decrease in heart rate. Within five minutes the blood pressure and heart rate returned to or toward control. Pronethalol produced ENE reversal (an increase rather than a decrease in blood pressure following the injection of ENE) (fig. 4), increased the pressor response to E, markedly reduced or abolished the depressor response to ISOP (ISOP modification), and had no effect on or slightly increased the pressor response to NE. The tachycardia following ISOP, ENE and E was also diminished or abolished by pronethalol.

Pronethalol increased the arrhythmia threshold dose of E, NE, ISOP, and ENE to eight times that of control (range of 4 to 16 times) in nine of ten animals (fig. 4). The antiarrhythmia duration of action of 2.5 mg./kg. of pronethalol was 15–25 minutes while the duration of action of 10 mg./kg. varied from 1–2.5 hours. In seven of ten animals given 2.5 mg./kg. of pronethalol, although the arrhythmia threshold for the catecholamines returned to control after 15–25 minutes, ENE reversal persisted for another 20–30 minutes. There was also partial restoration of the ENE-induced tachycardia. The injection of another 2.5 mg./kg. of pronethalol increased the catecholamines arrhythmia threshold, prevented the ENE-induced tachycardia and had no effect on or slightly increased the magnitude of ENE reversal.

Effects of Isoproterenol (milligram doses). The injection of 0.5–1 mg./kg. of ISOP produced a 40–60 per cent fall in blood pressure, a 25–50 per cent increase in heart rate and cardiac arrhythmias for 10–20 minutes. This dose of ISOP produced ENE reversal, decreased the depressor response to ISOP (micro-
gram doses) and increased the pressor response to E. The tachycardia produced by these agents was diminished or abolished. However, the arrhythmia thresholds for E, NE, ISOP and ENE were unchanged. Repeating the 0.5–1 mg./kg. of ISOP again produced a fall in blood pressure. The injection of 3 mg./kg. of ISOP produced results similar to those described for 0.5–1 mg./kg. in terms of (1) the effects on blood pressure, heart rate and cardiac rhythm and (2) modification of the responses to E, NE, ENE and ISOP. However, the arrhythmia thresholds of these four agents were increased to a level four times greater than control in four of five animals. In addition, the injection of 1 mg./kg. of ISOP now produced a 10–20 per cent rise in blood pressure ("ISOP (1 mg./kg.) reversal") (fig. 5). The injection of 1 mg./kg. of ISOP after 2.5 mg./kg. of pronethalol produced a depressor response. However after 10 mg./kg. of pronethalol, the injection of 1 mg./kg. of ISOP produced "ISOP (1 mg. kg.) reversal."

**Discussion**

The purpose of these experiments was to determine the role, if any, of the alpha adrenergic and beta adrenergic receptors in the production of cyclopropane-catecholamine arrhythmias. According to Ahlquist, myocardial ectopic excitation is attributable to the alpha adrenergic system. This concept appears to be supported by the observation that the cyclopropane-epinephrine arrhythmias are blocked by the alpha adrenergic blocking agent dibenamine. Interpretation of this observation to determine the mechanism of block by dibenamine is difficult for several reasons. It has been reported that the dose of dibenamine required to block the cyclopropane-epinephrine arrhythmia is greater than that required to produce E reversal. Since the dose of dibenamine which produces E reversal may only inhibit 50 per cent or less of the vasoconstrictor action of E, it is possible that a larger dose of dibenamine, which produces a full alpha adrenergic blockade, is required to prevent the cyclopropane-epinephrine arrhythmia. On the other hand, it has been reported that the dose of dibenamine required to block the cyclopropane-epinephrine ventricular fibrillation is less than that required to produce E reversal. In any case, the relationship between the antiarrhythmic and E reversal dose of dibenamine does
Fig. 4. Effect of pronethalol on ethynorepinephrine (ENE) arrhythmic threshold. **Panel A.** Injection of ENE (25 μg./kg.), at arrow, produced a fall in arterial pressure and cardiac arrhythmia. **Panel B.** Persistence of arrhythmia. Between panels B and C pronethalol (10 mg./kg.) given. **Panel C.** Injection of ENE (25 μg./kg.), at arrow, produced an increase in arterial pressure (ENE reversal) but a normal sinus rhythm was maintained. **Panel D.** ENE reversal and normal sinus rhythm after ENE (200 μg./kg.).

Not permit conclusions as to the specificity of the antiarrhythmic action of dibenamine since the dose of dibenamine required to block E induced vasoconstriction may differ from the dose required to block other alpha stimulating effects of E.

Another problem of interpretation concerns the use of E as the test drug. Dibenamine

Fig. 5. Isoproterenol (ISOP) (1 mg./kg.) reversal. **Panel A.** ISOP (1 mg./kg.), at arrow, produced fall in arterial pressure. Between panels A and B ISOP (3 mg./kg.) given. **Panel B.** ISOP (1 mg./kg.) produced an increase in arterial pressure.
markedly changes the blood pressure effects of E. Although there are some differences of opinion as to the importance of blood pressure changes in the genesis of the cyclopropane-epinephrine arrhythmias, most investigators have found that the blood pressure effects may have a role. Therefore part of the arrhythmogenic action of dibenamine could be attributed to its modification of the pressor effect of E.

A final problem is the marked variation in threshold dose of E required to produce cardiac arrhythmias. If a single dose is compared before and after dibenamine, an antiarrhythmic effect could be missed or misinterpreted. If the E threshold dose for arrhythmia was 0.125 μg./kg., but the test dose was 1 μg./kg., a fourfold increase in threshold following dibenamine could be missed. If the threshold dose and test dose happened to coincide, an antiarrhythmic effect would be observed, but the magnitude would not be known and a meaningful comparison with other agents could not be made.

The present experiments were designed so as to minimize these problems as much as possible. Although 2.5 mg./kg. of dibenamine produced E reversal, 20 mg./kg. of dibenamine was given. An attempt was made to circumvent the blood pressure problem by using ISOP and ENE, which produced cardiac arrhythmias even though the blood pressure fell. NE was also studied since its blood pressure rise, although diminished after dibenamine, was not reversed. Manipulation of the blood pressure by aortic constriction permitted further insight into the role of blood pressure. Finally, the determination of arrhythmia thresholds permitted a comparison between dibenamine and pronethalol.

In the present study dibenamine did not consistently modify the arrhythmia threshold for cyclopropane-catecholamine arrhythmias. The cyclopropane-epinephrine arrhythmia, which was the most commonly affected arrhythmia, showed a modest increase in threshold in approximately 50 per cent of the animals. The arrhythmia thresholds for NE, ENE, ISOP were less frequently increased by dibenamine. The increase in threshold with E was in part attributable to E reversal since prevention of E reversal by aortic constriction could, in some animals, abolish the antiarrhythmic effect of dibenamine. Dibenamine could, in the same animal, produce E reversal and raise the arrhythmia threshold for E, but not change the arrhythmia threshold for ISOP, ENE or NE. These results could also be attributed to the different blood pressure effects of dibenamine on E, NE, ENE and ISOP. The relationship between blood pressure and cardiac arrhythmias can further be seen in the experiments in which aortic constriction decreased the arrhythmia threshold dose of ISOP.

Although the blood pressure can in some instances affect the arrhythmia threshold, in many cases the arrhythmia is independent of the blood pressure effects. In approximately half the animals the arrhythmia threshold for E was unchanged despite the dibenamine induced E reversal. In some animals an increase in arrhythmia threshold occurred which could not be attributed to the blood pressure effects of dibenamine. This may be a manifestation of the direct myocardial effects of dibenamine.

In summary, the results with E, NE, ENE, ISOP and dibenamine suggest that (1) changes in arterial pressure affect the cyclopropane-catecholamine arrhythmia threshold in some animals but not in all animals; (2) dibenamine does not consistently elevate the arrhythmia threshold; (3) when dibenamine does increase the arrhythmia threshold it is usually only a twofold increase and is frequent, but not always, attributable to modification of the blood pressure response to the catecholamines; (4) modification by dibenamine of the blood pressure response to the catecholamines does not consistently change the cyclopropane-catecholamine arrhythmia threshold.

Pronethalol consistently increased the cyclopropane-catecholamine arrhythmia threshold to a level 8 times greater than control. Associated with this action was a beta adrenergic blockade (determined by ENE reversal and ISOP modification) and prevention of the ISOP and ENE increase in heart rate. The time of onset and wearing off of these three effects were often similar. However in some animals there was a dissociation between ENE reversal and the increase in arrhythmia threshold. Just as E reversal may not indicate a full alpha adrenergic block, ENE reversal may not
indicate a full beta adrenergic block. In addition, the dose of pronethalol required to produce a beta adrenergic vascular block may differ from that required to produce a beta adrenergic myocardial block. Before the increase in arrhythmia threshold produced by pronethalol could be attributed to a specific myocardial beta adrenergic blockade, a non-specific antiarrhythmic effect of pronethalol must be ruled out. The beta adrenergic blocking agent DCI also blocks cardiac arrhythmias. However, Lucchesi and Hardman showed that DCI possesses an antiarrhythmic action which is independent of its ability to block beta adrenergic receptors. Somani and Lum questioned whether the antagonism of adrenergically induced arrhythmias by DCI and pronethalol was an expression of specific adrenergic blockade since both agents were capable of suppressing the ventricular tachycardia produced by ouabain. In addition, pronethalol was shown to possess a direct depressant action on atrial and ventricular musculature comparable to that of quinidine. For these reasons the experiments with mg. doses of ISOP were undertaken. With 0.5–1 mg./kg. of ISOP a beta adrenergic block was produced, using the criteria of ENE reversal and ISOP modification. No change in the arrhythmia threshold was observed. However, this dose of ISOP did not convert the depressor response to 1 mg./kg. of ISOP to a pressor response. Increasing the dose of ISOP to 3 mg./kg. now produced "ISOP (1 mg./kg.) reversal" in addition to ENE reversal and ISOP modification. A similar beta adrenergic blocking action and alpha receptor activation produced by mg. doses of ISOP was reported by Butterworth. The beta adrenergic blocking action of 3 mg./kg. of ISOP produced a 4-fold increase in the cyclopropane-catecholamine arrhythmia threshold. Pronethalol (2.5 mg./kg.) and ISOP (0.5–1 mg./kg.) produced ENE reversal and ISOP modification but not "ISOP (1 mg./kg.) reversal." The latter could be produced by 10 mg./kg. of pronethalol or by 3 mg./kg. of ISOP and may be a better criterion of beta adrenergic blockade than ENE reversal and ISOP modification. Both doses of pronethalol (2.5 and 10 mg./kg.) increased the arrhythmia threshold while only the larger dose of ISOP increased the arrhythmia threshold. This, as well as the greater increase in threshold with pronethalol, may be attributed to the beta adrenergic blocking and myocardial depressant effects of pronethalol as compared with the beta adrenergic blocking and myocardial stimulating effects of mg. doses of ISOP. These results suggest that the cyclopropane-catecholamine arrhythmias are blocked by specific beta adrenergic blockade and that myocardial ectopic excitation may be attributable to the beta adrenergic receptors.

Summary

Cardiac arrhythmias were produced in the cat by the injection of E, NE, ENE or ISOP during the inhalation of 25 per cent cyclopropane in oxygen. The injection of dibenamine, an alpha adrenergic blocking agent, produced E reversal, decreased the pressor response to NE and increased the depressor response to ISOP. Dibenamine did not consistently increase the threshold doses of catecholamines required to produce cardiac arrhythmias. In those instances where the arrhythmia threshold doses of the catecholamines were increased, usually to twice control, this result often was attributable to a modification of the blood pressure effects of the catecholamines by dibenamine. The beta adrenergic blocking agent pronethalol produced ENE reversal, increased the pressor response to E and markedly reduced or abolished the depressor response to ISOP. The arrhythmia threshold doses of the catecholamines were increased to 8 times that of control. Large doses of ISOP (3 mg./kg.) produced a beta adrenergic blockade and increased the arrhythmia threshold doses of the catecholamines to four times that of control. The results suggest that the cyclopropane-catecholamine arrhythmias are blocked by specific beta adrenergic blockade and that myocardial ectopic excitation may be attributable to the beta adrenergic receptors.

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HYPERTHERMIA

Prevention depends primarily upon awareness of the anesthesiologist. Any patient exhibiting a preoperative temperature elevation should be carefully evaluated. If the procedure is elective, operation should be postponed until the temperature is normal and the cause for the elevation is known. If the temperature elevation is secondary to the disease process for which surgery is being done, and preoperative attempts to lower it have been unsuccessful, then direct cooling along with antishivering agents can be used during anesthesia. A nonbreathing system, hydration, sparse drapes, and avoidance of belladonna drugs are useful adjuvants. Treatment of acute intraoperative hyperthermia involves four considerations: (1) Lowering the temperature, either by instillation of cold solutions into the peritoneal cavity if the abdomen is open, or by the direct application of ice. (2) Treatment of metabolic and respiratory acidosis. Accurate estimation of acidosis may best be accomplished by determination of arterial pH and Pco₂. (3) Prevention of hypoxia. (4) Treatment of hypovolemia by the rapid administration of large volumes of Ringer's lactate solution. (Saidman, L. J., and others: Hyperthermia During Anesthesia, J.A.M.A. 190: 1029 (Dec. 21) 1964.)