Effects of Inhalation Anesthetics on the Myocardial Catecholamines and its Response to Norepinephrine

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(Received for Publication: December 10, 1966)

ABSTRACT

The data obtained from present experiments demonstrated that among several inhalation anesthetics, ether was the most irritable, resulting in marked irregularity of respiratory movement, and halothane depressed respiratory rate more than the other. The pulse rate and blood pressure were decreased markedly in ether and the halothane anesthesia. The rate of beat of the isolated atria was not greatly altered after anesthesia with ether or trichlorethylene, while it was reduced after chloroform or halothane inhalation. The response of isolated atria to exogenous norepinephrine was most prominent in the atria isolated from halothane anesthetized rabbits. Myocardial catecholamine contents were reduced uniformly after anesthesia with each anesthetic and most significantly with the halothane inhalation. From the above results, it may be concluded that the increasing cardiac activity with general inhalation anesthetics is closely related to the quantitative changes of the endogenous myocardial catecholamine contents.

INTRODUCTION

The growing frequency of cardiac arrest during anesthesia and surgery has been the subject of considerable discussion in recent years. In 1954, the study of Beecher and Tood was very illustrative. In their analysis of 599,548 anesthetics, they calculated that one death in 420 operations resulted from surgical errors, whereas death due primarily to the anesthesia was estimated at one per 2,680 anesthetics, and the anesthetic technique was an important contributory causes of death in one per 1,560 cases.

It has been well known that the poor risk patients including the geriatric, pediatric and congenital or acquired heart anomaly groups contributed greatly to the surgical fatalities. Because of the toxicity of the general inhalation anesthetics, chloroform with its strong cardiotoxicity was limited to use in local clinics, and trichlorethylene with the action of partial metabolism and accumulation in the body limited its use to less than two hours. Halothane also with possible hepatotoxicity was considered contraindicated for use clinically on jaundice patients. Although ether has various side actions, it became popularized in many clinics because of the large safety margin.

Sadove and Natof (1958), and Engel and Secher (1959) pointed out several precipitating factors in cardiac arrest from anesthetic techniques; hypoxia, hypercarbia, overdose of anesthetic agents, hemorrhage, hypotension, reflex activity and hypothermia. Many causative factors have been reported by the experimental or clinical study of cardiac arrest. If such a dangerous complication occurred, it was very difficult to treat. Recently various special operating room monitorings were developed and it should re-
duce the mortality if the resuscitation has not been delayed. However, it is still uncertain how to treat it most effectively or what is the mechanism of the cardiac arrest.

During recent years, important factors of cardiac arrhythmias and arrest under general inhalation anesthetics have been demonstrated to be related to increasing sensitivity of the sympathetic nervous system by the study of Price et al. (1959), Hamelberg et al. (1960), and Li and Esten (1960). On the other hand, cardiac arrhythmias and arrest during anesthesia were much improved with beta-adrenergic receptor blockade, and this has been correlated with the effect of the myocardial, catecholamines by the study of Payne (1963) and Johnstone (1960a). Furthermore the relationship between the ventricular fibrillation under hypothermia and the myocardial catecholamines was demonstrated by the study of Lee (1963) in our department.

The sympathetic nervous system has been known to be a factor in the producing of cardiac arrest, especially, when cardiac muscle has been previously sensitized by the general inhalation anesthetics.

The present study was undertaken to investigate the relationship between cardiac sensitivity to norepinephrine and the myocardial catecholamines contents during general inhalation anesthesia.

MATERIAL AND METHODS

Rabbits weighing 2.0 kg were fixed on the table in supine position. Endotracheal tubes were inserted following tracheotomy. Inhalation anesthetic agents with oxygen were administered by a non-rebreathing system with Wright-Belton or Stephen-Slater valves connected with a heidbrink anesthesia machine. The left carotid artery was exposed and heparine (0.5 mg per kg) was injected, then the glass canule was inserted to artery and connected with a mercury manometer for continuous recording on a smoked drum of the changes in arterial blood pressure and the changes of the respiration and pulse rate were determined at intervals of 10 minutes.

Deep anesthesia (Stage 111, plane 2 or 3) was maintained for two hours. After two hours of anesthesia, the chest was opened and the heart was immediately removed.

The atria isolated from the ventricles, were suspended in the muscle chamber containing 100 ml of Tyrod's solution maintained at the constant temperature of 38°C, with full oxygenation.

Norepinephrine was added to the chamber and the changes of atrial beat and contractile amplitude were expressed as per cent changes relative to those prior to the addition of the drug.

The catecholamine contents of the cardiac muscle were determined by the Amico-Bowman Spectrophotofluorometric procedure described by Shore and Olin (1958).

RESULTS

The changes of respiration, pulse rate and blood pressure were shown in figure 1 during two hours of anesthesia with ether, trichlorethylene, chloroform and halothane in the rabbit.

At the end of 2 hrs of anesthesia, the animals were killed and the response to norepinephrine of their isolated atria and their myocardial catecholamine contents were determined and summarized in figures 2 and 3 and table 1.

With ether inhalation (10%), it took thirty minutes to reach deep anesthesia. During the initial thirty minutes, the respiratory rate was rapid and irregular, but under deep anesthesia, respiration became stabilized although the rate remained rapid throughout. The pulse rate was rapid and the blood pressure was continuously decreased by about 60% compared with normal controls at the end of anesthesia. The rate in response to norepinephrine in the isolated atria after two hours of anesthesia with ether was.
Fig. 1. Changes of respiration, pulse and blood pressure.

Inhalation of trichlorethylene (0.5–1.0%) promptly induced deep anesthesia and calm anesthesia without association of irregularity or increased rate of respiration. The pulse rate and blood pressure were gradually decreased. Especially blood pressure was decreased by about 40% below normal controls. The isolated atrial rate was moderately decreased but the atrial response to norepinephrine was moderately increased. Nevertheless, the myocardial catecholamine contents were decreased slightly below normal controls.

Inhalation of chloroform (0.5–1.0%) took forty minutes to produce deep anesthesia. Until then, respiration was rapid and irregular, but when deep anesthesia had been established, the respiration became calm and regular. The pulse rate was rapid and the blood pressure was slightly decreased by about 20% of the normal controls. The rate of the isolated atria after chloroform anesthesia was reduced moderately. However, the rate response to norepinephrine was slightly increased while amplitude response increased more than five times in low concentration over that of normal. The myocardial catecholamine contents were decreased by one and a half of the normal controls.

Inhalation of halothane (1.0–2.0%) gave a similar induction course to chloroform except a somewhat shorter time was required to reach deep anesthesia and the respiratory rate was sli-

Table 1. Comparison of myocardial and adrenal gland catecholamine contents

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Exp</th>
<th>Initial rate of contraction (beat/min)</th>
<th>Catecholamine</th>
<th>Concentration (μg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myocardium</td>
<td>Adrenal gland</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NE</td>
<td>E</td>
</tr>
<tr>
<td>None</td>
<td>10</td>
<td>168±9.41</td>
<td>1.74±0.11</td>
<td>0.99±0.003</td>
</tr>
<tr>
<td>Ether</td>
<td>8</td>
<td>153±11.23</td>
<td>1.20±0.06</td>
<td>0.88±0.001</td>
</tr>
<tr>
<td>Trichlorethylene</td>
<td>8</td>
<td>163±6.24</td>
<td>1.51±0.06</td>
<td>0.99±0.001</td>
</tr>
<tr>
<td>Chloroform</td>
<td>8</td>
<td>145±8.50</td>
<td>0.95±0.06</td>
<td>0.80±0.002</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>8</td>
<td>121±6.45</td>
<td>0.18±0.04</td>
<td>0.80±0.001</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
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MYOCARDIAL CATECHOLAMINES AND ITS RESPONSE TO NOREPINEPHRINE

Fig. 2. Cardiac rate and amplitude response to norepinephrine.

Fig. 3. Changes of myocardial and adrenal catecholamine contents

Slightly decreased until the end of anesthesia. The pulse rate was slow with depression and the blood pressure moderately decreased by about 30% of the normal controls. The isolated atrial beat was significantly decreased compared to other inhalation anesthetics, but the rate with norepinephrine was increased one and a half times and furthermore amplitude response increased significantly. The myocardial catecholamine contents were decreased by one and a half of the normal controls.

DISCUSSION

In general, small animals such as rabbits are well known to be very sensitive to the anesthetic agents, although the etiology is still in debate. As for respiration in rabbits demonstrated in the present experiments, it increased with ether inhalation, but decreased with chloroform and halothane, while in the anesthetia of trichloroethylene no visible changes were observed.

During recent years, a detailed description of the factors increasing respiration in ether anesthesia has been made by Dripps and Severinghause (1955), and of the factors causing inhibition with chloroform and halothane, by Ravenos (1956), Devine et al. (1958), Hall et al. (1958), and Severinghause and Cullen (1958). Whitteridge et al. (1944), after the study of the vagus nerve in rabbits, stated that the rapid but shallow respiration was due to the stretch receptors which had been stimulated by trichloroethlene. According to the report of Dundee (1953) and Dripps et al. (1955), respiration rate in a man
under anesthesia with trichloroethylene is accelerated to twice normal. What was interesting, however, was that no increase was observed in this experiment using rabbits. This difference is considered to be due to the variation in sensitivity of the respiratory system in the different species.

During two hours of anesthesia in rabbits, the pulse and blood pressure were measured at short intervals and the result showed an uniform tendency to decrease in both.

According to Brewster et al. (1963), cardiac output is increased during the initial stage of ether anesthesia in dogs owing to stimulation of the sympathetic nervous system. However, as the anesthesia is deepened myocardial catecholamine contents are reduced because of the increasing plasma ether concentration, and at the end cardiac activity is eventually inhibited.

Clinically, decrease of cardiac output in a man following ether anesthesia was reported by Johnstone in 1951. Price et al. (1959) having observed that the cardiac output under ether anesthesia was still decreased with bilateral adrenalectomy, pointed out that obviously, its decrease was not due to the adrenal medulla but probably due to the action of the sympathetic nervous system. In recent years, however, it has been emphasized by Li et al. (1964) that the changes in myocardial catecholamine content in ether anesthesia are closely related to the consumption of the catecholamine reservoir in the adrenal medulla.

In 1911, Leven and Lewis suggested ventricular fibrillation as a causative factor of cardiac arrest occurring during chloroform anesthesia, and the etiology was attributed to increased cardiac sensitivity to circulating epinephrine, whether it was exogenous or endogenous.

As for halothane anesthesia, McLoed and Reynolds (1964), with their experiments using cats, demonstrated that the ventricular arrhythmia occurring with halothane inhalation was due to the increased ventricular autosensitization, which had been caused by the action of endogenous acetylcholine. However, Raventos (1956) and Hall and Norris (1958a) insist on the action of sympathetic nervous system as a leading. Incidentally, Payne in 1963 stated that the imbalance of the cardiac autonomic nervous system resulting from the decreased tension of parasympathetic nervous system, had brought a similar inhibitory picture. Though it has not been fully clarified in the present experiments, the cardiac inhibition caused by the toxicity of anesthetic agents themselves is considered to be a main factor.

The fact that the myocardial and adrenal catecholamine contents were markedly reduced after anesthesia in the present experiments, tells us that anesthetic agents are in someway related to cardiac inhibition. In 1963, Lee in our department reported that the reduction of myocardial catecholamine contents under hypothermia had a close connection with the inhibition of cardiac activity. On the other hand, Li et al. (1964) demonstrated that in dogs under ether anesthesia epinephrine content in the heart was obviously reduced while norepinephrine increased. In halothane anesthesia, however, the norepinephrine content in the myocardium was not at all changed, nor was epinephrine significantly altered in comparison with normal controls. They finally concluded that the increase in myocardial norepinephrine content in ether anesthesia was due to the accelerated action of the postganglionic fibers of the parasympathetic nervous system. From all of the above statements, we can easily postulate that the cardiac activity during anesthesia is closely related to the circulating catecholamines.

Inhalation of ether, in its early stage, gives a possibility of cardiac inhibition, which is caused by the pulmonary carotid reflex or increased susceptibility of systemic baroreceptors (Robertson et al. 1956), but in general ether, unlike
the derivatives of hydrocarbon in the halogen system, has not been known to sensitize the cardiac conducting system (Li et al. 1964).

In the present experiments, the pulse rate of the isolated atria under ether anesthesia was not significantly decreased, nor was the rate in response to norepinephrine notably altered compared to those of normal controls, even though the high catecholamine content in the blood could be easily anticipated from the considerably reduced myocardial and adrenal catecholamine contents.

On the other hand, chloroform and halothane reduced the rate of the isolated atria of rabbits, but increased the rate in response to norepinephrine. This result corresponds to the early reports on the specific cardiotoxicity of chloroform by Levy et al. (1911), Grollman et al. (1947), and Guedel (1937).

Halothane, which had been synthesized by Suckling through 1951 to 1956, was welcomed as an excellent anesthetic agent having the possibility of covering the weak points of chloroform. However, in recent months, many reports have been made, stating that it is not an exception to producing arrhythmias by increasing the cardiac sensitivity to catecholamine (Hall & Norris, 1958a, Price et al., 1958, and Andersen & Johnson 1963). Such an accelerating action was observed in the present experiments also, and the catecholamines being mostly released in the circulating system, were reduced in the myocardial tissues and adrenal medulla as with chloroform anesthesia. The mechanism of myocardial epinephrine is not clearly understood but the following possibilities are considered in explanation: (1) Increased utilization of epinephrine to support the cardiovascular system during anesthesia; the rate of utilization or "breaking down" of epinephrine exceeds the rate of biosynthesis; (2) Epinephrine may be exhausted because of its release from the chromaffin tissue or less likely from the storage compartments at the nerve endings during anesthesia; (3) Anesthetic agents may block methylation of norepinephrine; (4) Epinephrine in the myocardial tissues may depend upon the adrenal gland for a supply of fresh epinephrine to be transported and deposited at the nerve endings; during ether, cyclopropane or halothane anesthesia, this supply may be interrupted, and hence a reduced source of epinephrine for the cardiovascular tissues.

In the present experiments, the decrease in myocardial catecholamine content was easily anticipated because it had been released into the blood as anesthesia was deepening. Therefore, with the aid of the reports that cardiac activity is closely related to the catecholamine content, by Dornhorst et al. (1962), Black et al. (1962), William et al. (1963), Payne (1963), Johnstone (1964a), and Duncan et al. (1963), it might be concluded that catecholamines released from the myocardial tissues after inhalation of anesthetic agents had a great deal to do with the cardiac activity.

Another point to be emphasized in these experiments is that as myocardial catecholamine content decreases with various anesthetic agents, the response to norepinephrine is considerably increased particularly in anesthesia with the agents of the halogen system.

Much effort has been made to seek for the actual function of epinephrine in the myocardium, since Meek (1941), Dawes (1952), and Ricker et al. (1955) reported that it was the main factor increasing myocardial sensitivity. The anesthetic agents in the halogen system cause catecholamine to be released from the myocardial tissues, and secondarily to increase cardiac activity. Incidentally, as the released catecholamines, especially norepinephrine and epinephrine, are not taken up and the content in the blood is raised, the cardiac activity becomes more accelerated.

Accordingly, the increased cardiac sensitivity to norepinephrine is considered to have a very close relationship to the changes in myocardial catecholamine content. Of course, it is not pos-
sible as yet to conclude that the increase myocardial sensitivity is entirely due to the increased content of myocardial catecholamine or that of circulating catecholamine itself. However, it might be rather reasonable to explain it in this way; the anesthetic agents themselves influence the cardiac receptors or myocardial protein or MAO, which are directly related to norepinephrine and epinephrine, and therefore the sensitivity to norepinephrine becomes enhanced. Katz in his report in 1965, gave a similar opinion, that cardiac sensitization is not entirely dependent catecholamine. Among the anesthetic agents in the halogen system, only trichloroethylene did not seem to influence respiration and cardiac activity excluding the tendency to inhibition accompanied by spontaneously in the course of anesthesia. Contrary to the high frequency of arrhythmia proved clinically by Hewer et al. (1941), Water et al. (1943), and Barnes et al. (1944), the present experiments showed no significant changes in cardiac sensitivity to norepinephrine in isolated atria, particularly after completion of anesthesia. Therefore, this is considered to be a point that should be further studied and discussed. Moreover, it seems to be demonstrated that only trichloroethylene among those anesthetic agents used in these experiments, has little influence on the catecholamine content in either myocardial or adrenal tissues.

REFERENCES

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