THE EFFECT OF INHALATIONAL ANESTHETIC AGENTS ON THE MYOCARDIUM OF THE DOG *

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INTRODUCTION

It was noted, in the course of demonstrations of the heart-lung preparation to students (1), that small amounts of ether caused significant dilatation of the isolated heart of the dog. A preliminary search of the literature and common texts of pharmacology and anesthesiology was surprising in the dearth of information available on the direct effects of inhalation anesthetic agents on the tone of the heart muscle. Frequently the lack of such information was interpreted as evidence that there is no effect. Much work has been done on the effect of these agents on irritability and rhythm of the heart. The greater relative importance of disorders of rhythm and their relation to possible sudden death has undoubtedly overshadowed and led to the neglect of the tone of the heart muscle.

Chloroform—Of all the inhalation agents, chloroform is the only one universally recognized for its direct depressant effect on the heart as well as its tendency to produce arrhythmias.

MacWilliam (2) in 1890 established this in his study on the open chests of cats. Direct mechanical recordings were made from the auricles and ventricles. He concluded, “Chloroform acts upon the heart; it causes a marked depression of the cardiac muscle, involving a reduction of its tone, a relaxation of the cardiac walls, and an impairment of their functional efficiency.” Gaskell and Shore (3), Embley (4) and Sherrington and Sowton (5) confirmed and extended MacWilliam’s basic observations. Cushney (6) has summarized these well in his current textbook of pharmacology.

Ether—Cattell (7) reviewed the literature to 1923 and investigated carefully the sites and nature of action of ether on the entire circulatory system. Using the pericardial sac as an oncometer he made heart volume records on cats. He noted, “From the beginning of the administration of ether there is relaxation of heart tone as indicated by

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increased volume. This becomes progressively greater as anesthesia becomes deeper, the maximum dilatation being reached only with the death of the animal.’’

Olmsted and Ogden (1) noted that two or three breaths of ether in the dog heart-lung preparation produced marked but transitory increase in volume. Bhatia and Burn (8) presented a similar tracing and reported a blood pressure drop and volume increase which persisted for a considerable time after the administration of ether for as little as eighty seconds.

Most of the current texts on pharmacology or anesthesia convey the impression that ether has no effect except at levels greater than the anesthetic range when it does cause dilatation and weakening of cardiac tone (9, 10). We have undertaken some experiments to be described in an endeavor to correlate these effects with level of anesthesia as determined by blood ether levels.

Cyclopropane—The prominence of rhythm and rate changes and their relative greater importance when this agent is employed had led to neglect of heart volume studies. A notable exception is the work of Brace, Scherf and Spire (11) who took cardiac plethysmograms on dogs under high concentrations of cyclopropane (50 to 75 per cent). They observed a marked dilatation which disappeared about twenty seconds after the gas was stopped and concluded, ‘‘There is a dilatation of the heart with an augmented output, but an increasing systolic inefficiency during administration of 50 per cent or 75 per cent cyclopropane.’’

So far as could be discovered, no work has been done on the effect of this agent on heart size in normal anesthetic ranges.

Divinyl Ether—There has been little or no work published on the effect of divinyl ether on the tone of the heart muscle. Textbooks either have omitted any reference to the subject, or have said that the heart is unaffected (6, 9, 10).

Nitrous Oxide—No direct effects of nitrous oxide on the heart in the absence of hypoxia have been described (6). Ward and Wright (12) produced consistent electrocardiographic changes from the administration of pure nitrous oxide, but these changes disappeared when slight amounts of oxygen were added.

Methods

The Starling heart-lung preparation was used to eliminate reflex control of the heart rate and to enable the observations to be carried out under controlled conditions of input-loads and resistance-loads. Aortic pressure was measured and recorded graphically by means of a damped mercury manometer connected to the aortic cannula, with a side arm. Right atrial pressure and pulmonary arterial pressures were measured by means of damped water manometers connected with
cannulas inserted into the right atrium by way of the inferior vena
cava and into the branch of the pulmonary artery to the left upper lobe.
Ventricular volume was measured by means of a Henderson cardi-
ometer and a piston type volume recorder, and was recorded mechani-
cally upon smoked kymograph paper. Left ventricular output minus
the coronary flow was measured either by a graduated cylinder and a
stop-watch or by a continuously recording flowmeter.

The anesthetic agents were administered by way of the pump main-
taining the pulmonary ventilation. In the experiments on ether, blood
ether levels were determined by the Schaffer-Ronzoni procedure (13).
Neither the venous return nor the peripheral resistance varied during
the course of an experimental observation. Thus the heart was called
upon to do a constant amount of work throughout any one experimental
period.

**Observations**

*Chloroform*—In each of three experiments on three heart-lung
preparations the usual effect on heart volume was noted with chloro-
form. There was marked dilatation with increased pulmonary pres-
sure and right auricular pressure. The volume never returned com-
pletely to the base level after the administration of chloroform was
stopped, which suggests some degree of permanent impairment of
myocardial tone under these conditions. Figure 1 illustrates the ef-

![Image of a graph showing volume changes during chloroform administration]

**Fig. 1.** Effects of chloroform. VV is cubic centimeter change in ventricular volume. The bottom of the stroke is systole and the top diastole. T is time in minutes. PP is pul-
monary pressure. AP is arterial pressure.
fect of but three breaths of chloroform. Administration in amounts similar to those used for other agents caused such dilatation that it was necessary to reset the piston recorder to keep the writing arm on the kymograph.

_Ether_—These experiments have been reported in detail previously (19). Thirteen heart-lung preparations were studied. Blood levels of ether corresponding to the various planes of anesthesia were obtained for each dog used for a heart-lung preparation before starting the surgical procedure involved in setting up the preparation. These levels were correlated with clinical signs of depth of anesthesia. Levels corresponded in general with those in the literature (14, 15, 16, 17, 18). These values were used for correlating effects on heart volume and efficiency with depth of anesthesia.

Definite cardiac dilatation was obtained with pre-anesthetic levels of blood ether. The dilatation increased progressively as the blood ether level increased. With blood ether levels corresponding to the second plane, there were beginning signs of dilatation beyond normal physiologic degrees, that is, the pulmonary and auricular pressure rose. With blood ether levels corresponding to the third plane these changes were pronounced. They were rapidly aggravated when the concentration of ether was pushed beyond this point.

_Cyclopropane_—Cyclopropane was mixed with oxygen in a calibrated gasometer as a rough index of concentration and the mixture

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**Fig. 2. Effects of cyclopropane.** VV is cubic centimeter change in ventricular volume. CO is cardiac output (75 cc. for each cycle). T is time in minutes. AP is arterial pressure. PP is pulmonary pressure.
was introduced through the pump maintaining respiration. Five experiments in five preparations were done. Mixtures of 10, 20, 30, 40 and 50 per cent cyclopropane were used. All produced some dilatation, but even with 50 per cent cyclopropane, ventricular volume plateaued before there was much rise in pulmonary or auricular pressure. In each case after the cyclopropane was withdrawn the heart volume returned to its base line. Figure 2 is a tracing made with 20 per cent cyclopropane. There was a maximal ventricular dilatation of 4 cc. Pulmonary pressure rose 7 mm. of water and auricular pressure rose 6 mm. of water.

**Divinyl Ether**—Unfortunately the means were not at hand to carry out quantitative studies with this agent, but two experiments in two preparations were done. The drug was vaporized on a piece of gauze over the pump intake by the open drop method. The smallest concentrations obtainable by this method produced some dilatation. On the other hand, with the greatest concentration we were able to achieve, the heart volume plateaued with only moderate rise in pulmonary pressure and no rise in auricular pressure. It is our impression that the relative degree of dilatation was greater than with cyclopropane, but not nearly so great as with ether. Figure 3 is an illustrative tracing. There was a ventricular dilatation of 14 cc. Pulmonary pressure rose 10 mm. of water.

**Nitrous Oxide**—Known concentrations of nitrous oxide and oxygen were mixed and introduced into the preparation by the same method as used for cyclopropane. Seven experiments in five preparations were

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**Fig. 3.** Effects of divinyl ether. VV is cubic centimeter change in ventricular volume. T is time in minutes. PP is pulmonary pressure. AP is arterial pressure in millimeters of mercury.
completed. Eighty per cent nitrous oxide consistently caused slight but definite dilatation. It was difficult to determine with certainty that the effect obtained was positively not the result of hypoxia. Stopping the pump to cause “apnea” also caused slight dilatation, not so great as occurred with nitrous oxide, but all changes were of such mild degree that results were equivocal. One hundred per cent oxygen caused no change. One hundred per cent nitrous oxide caused the most noticeable dilatation in this group, but still it was not great.

![Graph showing effects of nitrous oxide on ventricular volume and cardiac output](image)

**Fig. 4.** Effects of nitrous oxide. VV is cubic centimeter change in ventricular volume. T is time in minutes. CO is cardiac output (75 cc. for each cycle). PP is pulmonary pressure. AP is arterial pressure.

Sixty and forty per cent nitrous oxide caused slight dilatation. Figure 4 is a tracing made using 60 per cent nitrous oxide and 40 per cent oxygen. There was 3 cc. of ventricular dilatation. Pulmonary and auricular pressure did not change.

**DISCUSSION**

In the interpretation of these data one must bear in mind the physiologic mechanisms by means of which the heart adapts itself to varying loads under these conditions. A heart which is not failing, with a constant cardiac rate, will dilate in accordance with Starling’s Law whenever it is called upon to do more work; that is, if either the venous return or peripheral resistance is increased. On the other hand if the cardiac rate is constant and the work is maintained at a constant level, the heart will dilate whenever the efficiency of the myocardium is impaired.
In these experiments the rate, venous return and peripheral resistance were constant and volume changes of both ventricles were measured. An increase in ventricular volume could be caused by any of the three following mechanisms: (1) an impaired myocardial efficiency; (2) pulmonary vasoconstriction with consequent pulmonary hypertension and increased work of the right ventricle, and (3) coronary vasodilatation with an increased volume of blood in that part of the coronary system lying within the cardiometer. The second mechanism can be disregarded because there was always a considerable degree of dilatation before any rise in pulmonary pressure occurred. The third mechanism can be excluded because dilatation equal to a third of the initial volume of the heart could be produced and these extreme degrees of dilatation were usually accompanied by a drop in arterial and hence coronary pressure. Thus, we are left with the conclusion that any dilatation produced was the result of impaired myocardial efficiency.

Summary

The literature on the effect of some of the inhalation anesthetic agents on the tone of the heart muscle was reviewed briefly.

The effects of these agents were studied in the dog heart-lung preparation.

In this preparation chloroform causes rapid dilatation with early rises in pulmonary and auricular pressure.

Ether causes marked dilatation even in subanesthetic levels. Beginning with blood levels corresponding to second plane anesthesia this dilatation exceeds the physiologic as indicated by auricular and pulmonary pressure rises.

Cyclopropane in anesthetic range causes a definite dilatation, but not so marked as that produced by ether.

Divinyl ether was not studied quantitatively, but apparently causes a degree of dilatation greater than that produced by cyclopropane, but not nearly so great as that produced by ether.

Nitrous oxide causes slight cardiac dilatation even though administered with an adequate amount of oxygen.

These effects are the result of impairment of the efficiency of the myocardium.

References