A Comparative Study of The Effects of Five General Anesthetics on Myocardial Contractility:  

I. Isometric Conditions  

Burnell R. Brown, Jr., M.D., Ph.D.,* and J. Richard Crout, M.D.†

Isolated cat papillary muscles driven at a rate of 12 beats/min at 37.5°C were exposed to concentrations of cyclopropane, diethyl ether, halothane, and methoxyflurane similar to those required to produce general anesthesia in vivo. Each anesthetic depressed peak developed tension, maximal dp/dt, and the force–time integral of the twitch, and each shortened the time to peak tension. These variables were altered in qualitatively similar ways by all anesthetics tested, implying a common mode of action on the contractile process. When administered in equieffective concentrations from the standpoint of producing general anesthesia (i.e., at equal MAC’s), the order of activity of the anesthetics in depressing contractility (from most to least depressant) was: halothane > methoxyflurane > cyclopropane > diethyl ether. (Key words: General anesthetics; Myocardial contractility; Isometric.)

Several recent studies have described the depressant action of general anesthetics on the contractile performance of heart muscle in vitro. A question unresolved by these studies is whether different inhalational anesthetics depress heart muscle in qualitatively similar ways. If different anesthetics administered in

---

* Assistant Professor of Anaesthesia. Present address: Department of Anaesthesia, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts 02115.
† Associate Professor of Pharmacology and Internal Medicine, Burroughs-Wellcome Scholar in Clinical Pharmacology. Present address: Department of Pharmacology, Michigan State University College of Human Medicine, East Lansing, Michigan 48823.

Received from the Division of Clinical Pharmacology, Department of Pharmacology, and the Department of Anaesthesiology, The University of Texas Southwestern Medical School at Dallas, Texas 75231. Accepted for publication November 17, 1970. Supported by research grant GM-14439 and training grant GM-1421 from the National Institute of General Medical Sciences. Presented at the annual meeting of the American Society of Anesthesiologists in Washington, D.C., October 23, 1968.

---

Methods

Determination of Minimum Alveolar Anesthetic Concentrations in the Cat

To relate the potencies of anesthetics as depressants of myocardial contractility to their potencies as general anesthetics, it is necessary to expose papillary muscles in vitro to concentrations equal to those which produce general anesthesia in vivo. For this reason, the minimum alveolar concentrations (MAC) of each anesthetic necessary to prevent movement in response to clamping the tail was first determined in intact normal cats. These anesthetic concentrations (or multiples of them) were then used in in vitro studies of papillary muscles.

MAC values were determined as follows: Adult cats of either sex were fasted overnight. Each cat was then briefly anesthetized with

† Kindly supplied by Ohio Medical Products.
3–4 per cent halothane to permit insertion of an endotracheal tube. An 18-gauge Teflon catheter for obtaining end-tidal gas samples was inserted through the endotracheal tube to the carina. Anesthesia was then switched to the desired agent. To insure the attainment of equilibrium each animal was given an inspired concentration two or three times the anticipated MAC value for at least an hour before sampling began. Before the experiments began, gas chromatographic analysis showed no residual of the halothane used for the induction of anesthesia. Six hours were allowed to elapse before the determinations of methoxyflurane MAC were made. Body temperature was kept at 37–38°C with a heating blanket. Cats were periodically turned and their lungs hyperinflated to minimize microatelectasis. After one to six hours of anesthesia MAC was estimated by the method of Eger et al. Concentrations of anesthetics in end-tidal samples were determined on a Microtek GC-2500R gas chromatograph; standards supplied commercially by Ohio Medical Products were used to standardize the instrument.

**Papillary Muscle Apparatus**

Each cat was anesthetized with halothane, its heart extirpated, and the thinnest suitable right ventricular papillary muscle rapidly dissected free under oxygenated Krebs-Henseleit solution. One end of a fine gold chain was tied with thread to the tendinous end of the muscle and the other end was attached to a Statham Model UC2 force-displacement transducer. The base of the muscle (with a small accompanying portion of right ventricular wall) was placed in a muscle holder such that it was held against two punctate electrodes about 3 mm apart. Preparations were stimulated through the electrodes by square-wave pulses 1 msec in duration at voltages just above threshold (1–3 volts). The stimulus was provided by a Tektronix stimulator composed of a Type 161 pulse generator, a Type 162 waveform generator, and a Type 160 power supply.

Muscles were suspended in a modified Krebs-Henseleit solution of the following composition (mM) before equilibration with CO₂: Na⁺ 145, K⁺ 5.0, Ca²⁺ 2.5, Mg²⁺ 1.2, Cl⁻ 127, SO₄⁻ 1.2, HCO₃⁻ 25, glucose 10. Through a sintered glass disk, 95 per cent O₂–5 per cent CO₂ was bubbled into the solution; the resultant pH was 7.4. Random determinations of P₂O₃ with a Clark electrode (Radiometer Electronics, Copenhagen) showed the oxygen tension to be greater than 400 torr at all times. All experiments were conducted at 37.5°C at a contraction frequency of 12 beats/min.

The signal from the force-displacement transducer was sent into a Tektronix Type 3C66 carrier amplifier and displayed on a Tektronix Type 564 storage oscilloscope. This signal, in turn, was differentiated on a Tektronix Type 3A8 operational amplifier and displayed on the oscilloscope, along with the original signal and the stimulus signal. Photographs of the oscilloscope tracings were taken at appropriate intervals on Polaroid film with a Tektronix Series 125 camera.

The concentration of volatile anesthetic in the bath solution was controlled in the following manner: The inflow line of 95 per cent O₂–5 per cent CO₂ contained an in-line vaporizer, and the rate of flow through this vaporizer was monitored by a calibrated mass flowmeter (Matheson Co., Inc., East Rutherford, N. J.). Volatile anesthetics were injected into a side port in the vaporizer through a Teflon catheter connected to a gas-tight Hamilton syringe mounted in a Harvard variable-speed infusion pump. Anesthetic concentration was varied by changing the speed of the infusion pump. During an experiment the concentration was checked by gas chromatography every five minutes. In experiments with
cyclopropane, the anesthetic was delivered from a conventional anesthesia machine into the main inflow line of 95 per cent O₂–5 per cent CO₂. The flow rate was monitored with a mass flowmeter. In experiments with nitrogen, this gas was dispensed from a commercial C cylinder and its flow rate monitored in a similar manner.

Experimental Design and Analysis of Data

At the beginning of an experiment a papillary muscle was placed in the holder under minimal stretch and allowed to equilibrate in the bath for five minutes; the muscle was then stimulated electrically at a frequency of 12/min. Muscle length was increased by adjustment of a micrometer mount holding the force-displacement transducer until developed tension reached a maximum. An hour of equilibration time was then allowed. During this time some reduction in baseline usually occurred due to the slow stretching of elastic and viscous elements within the muscle, but at the end of this period the baseline was stable and the muscle was still operating at or near the peak of its length-tension curve. A control tracing was photographed and then one of the anesthetics under study was introduced into the system at a concentration of 1 MAC. After at least 20 minutes, when the contraction height had stabilized, the oscilloscopic tracing was again photographed. The concentration of anesthetic was increased to 2 MAC, then to 3 MAC; the tracing was photographed after attainment of the steady-state response to each concentration.

A typical isometric contraction is shown schematically in figure 1. The following variables in each photograph were measured: 1) the latency or interval of time between the electrical stimulus and the onset of contraction, in msec; 2) the peak developed tension (PDT), in g; 3) the maximal rate of change of tension (dp/dt max), in g/sec; 4) the time to peak tension (TPT), in msec; 5) the force-time integral (FTI), or total area under the curve from the onset of contraction to the point of peak developed tension (shaded area in figure 1); this was measured with a metric planimeter and expressed as g-sec.

Changes in each variable at the different anesthetic concentrations were expressed as per cent depressions from control. Dose–response curves as functions of anesthetic concentration were constructed for each of the five anesthetic agents. Statistical calculations were done by the University of Texas Southwestern Medical School Computer Center on an IBM 1800 computer.
Results

Minimum Alveolar Anesthetic Concentrations in the Cat

MAC values (as v/v per cent) for the five general anesthetics studied were (mean ± SE): cyclopropane, 19.7 ± 0.95 per cent; diethyl ether, 2.1 ± 0.1 per cent; Ethane, 1.2 ± 0.1 per cent; halothane, 0.62 ± 0.10 per cent; methoxyflurane, 0.23 ± 0.02 per cent. Six cats were used to determine each experimental value. Multiples of these MAC values were then used in the in vitro experiments. As an example, 1 MAC for halothane refers to 0.8 per cent, 2 MAC to 1.6 per cent, and 3 MAC to 2.4 per cent halothane.

Isometric Contractility Studies

Typical effects of diethyl ether and halothane on isometric contractions are shown in figure 2. Both anesthetics depressed PDT, dp/dt_max, TPT, and FTI. However, when these agents were given at equianalgesic concentrations (equal MAC values), halothane produced greater depression.

Thirty-eight muscles were studied in this manner, each at anesthetic concentrations one, two, and three times the MAC of the agent under consideration. To assure that observed changes in contractility were due solely to the anesthetics and were not modified by the release of norepinephrine from adrenergic nerve endings in the preparation,12 12 muscles were studied in the presence of dl-propranolol (5.2 × 10^-6 M added 15 minutes before the anesthetic was introduced into the system). This concentration of propranolol was sufficient to produce a 15-fold shift to the right in the dose-response curve for norepinephrine without causing a negative inotropic effect. The results (table 1) showed that changes in PDT, dp/dt_max, and FTI due to diethyl ether, cyclopropane, and halothane were not altered by β-adrenergic receptor blockade. (Methoxyl-

Table 1. Lack of Effect of Propranolol (5.2 × 10^-6 M) on Contractility Changes due to Anesthetics

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Concentration</th>
<th>Propranolol*</th>
<th>n</th>
<th>PDT</th>
<th>dp/dt_max</th>
<th>FTI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23 ± 1.5</td>
<td>14 ± 3.5</td>
<td>32 ± 2.6</td>
</tr>
<tr>
<td>Diethyl Ether</td>
<td>1 MAC</td>
<td>+</td>
<td>5</td>
<td>23 ± 1.4</td>
<td>15 ± 3.5</td>
<td>26 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>2 MAC</td>
<td>+</td>
<td>5</td>
<td>47 ± 2.1</td>
<td>30 ± 5.7</td>
<td>56 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>5</td>
<td>42 ± 3.9</td>
<td>28 ± 4.7</td>
<td>40 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>3 MAC</td>
<td>+</td>
<td>5</td>
<td>66 ± 2.4</td>
<td>48 ± 4.7</td>
<td>71 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>5</td>
<td>55 ± 5.2</td>
<td>40 ± 7.5</td>
<td>67 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>1 MAC</td>
<td>+</td>
<td>6</td>
<td>27 ± 3.7</td>
<td>21 ± 3.1</td>
<td>34 ± 4.6</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>3</td>
<td>35 ± 3.8</td>
<td>22 ± 4.0</td>
<td>37 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>2 MAC</td>
<td>+</td>
<td>6</td>
<td>43 ± 4.1</td>
<td>32 ± 3.4</td>
<td>54 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>3</td>
<td>49 ± 7.2</td>
<td>35 ± 7.5</td>
<td>54 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>3 MAC</td>
<td>+</td>
<td>6</td>
<td>60 ± 2.6</td>
<td>48 ± 4.1</td>
<td>68 ± 4.2</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>3</td>
<td>71 ± 15.0</td>
<td>46 ± 11.6</td>
<td>68 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>1 MAC</td>
<td>+</td>
<td>6</td>
<td>42 ± 5.2</td>
<td>31 ± 4.0</td>
<td>47 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>4</td>
<td>32 ± 1.4</td>
<td>28 ± 1.9</td>
<td>40 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>2 MAC</td>
<td>+</td>
<td>6</td>
<td>71 ± 5.4</td>
<td>61 ± 8.3</td>
<td>78 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>4</td>
<td>71 ± 2.4</td>
<td>58 ± 2.0</td>
<td>72 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>3 MAC</td>
<td>+</td>
<td>6</td>
<td>92 ± 3.0</td>
<td>83 ± 3.7</td>
<td>92 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>4</td>
<td>86 ± 1.4</td>
<td>77 ± 1.5</td>
<td>88 ± 0.9</td>
</tr>
</tbody>
</table>

* None of the means obtained in the presence of propranolol differed significantly from the corresponding values in the absence of propranolol.
flurane and \( \text{Ethrane} \) were not studied in this experiment. Since propranolol-treated and control muscles did not respond differently to anesthetics, the two groups were pooled for subsequent analysis of the data.

Each anesthetic produced dose-related depression of PDT, \( \frac{dp}{dt_{\text{max}}} \), FTI, and TTF, as shown in figure 3. Analyses of variance showed that the slopes of the regression lines in each panel of figure 3 do not differ from one another, with two exceptions. In figure 3A the slope for cyclopropane is different from those for halothane and \( \text{Ethrane} \) \( (P < 0.05) \). In vitro muscles are quite susceptible to changes in oxygen concentrations, since Krebs-Henseleit solution contains very little dissolved oxygen. Since hypoxia produces a modest positive inotropic response in cat papillary muscles, it is possible that the high concentrations of cyclopropane used in these experiments (39.4 per cent and 59.1 per cent at 2 and 3 MAC, respectively) caused sufficient hypoxia in the muscle to reverse partially the negative inotropic effect of the anesthetic. The slope for methoxyflurane is significantly greater than those for \( \text{Ethrane} \), cyclopropane, and ether \( (P < 0.05) \), as shown in figure 3B; the reason for this is unknown. As a further check of the similarity of the actions of these five anesthetics, the per cent changes in PDT and FTI of each twitch were plotted against the corresponding per cent change in \( \frac{dp}{dt_{\text{max}}} \), as shown in figure 4. There was a high positive correlation between these variables and the data for each anesthetic fell on a common regression line, indicating that changes in shape of the isometric contractility twitch are qualitatively indistinguishable from one anesthetic to another.

Each anesthetic produced a dose-dependent shortening of TPT, i.e., the contraction reached its peak height more quickly in the presence of the anesthetic (fig. 3D). However, the duration of the relaxation phase of contraction (i.e., the duration of the unshaded area under the curve in fig. 1) was not altered significantly by any of these agents. Neither did they change latency significantly from the normal value of approximately 35 msec.

**Relative Potencies**

The only difference found among these anesthetics was in their relative potencies. Their order of potency as depressants of myocardial contractility (EDC in table 2) paralleled their potencies as general anesthetics (with the exception of halothane and \( \text{Ethrane} \)), i.e., methoxyflurane \( \text{Ethrane} \) halothane \( > \) diethyl ether \( > \) cyclopropane. However, when viewed in terms of the degrees of depression produced by equianalgesic concentrations (i.e., by concentrations of 1 MAC, figure 3 and table 2), their order of activity (from most to least depressant) was: \( \text{Ethrane} \) halothane \( > \) methoxyflurane \( > \) cyclopropane \( > \) diethyl ether.

**Discussion**

Depression of myocardial contractility is one of the fundamental actions of inhalation general anesthetics. This effect is dose-related and reversible, and it can be demonstrated both in vitro and in vivo. The results of the experiments reported in this paper suggest that, in terms of muscle mechanics, the primary changes produced by anesthetics in the cat papillary muscle are depression of the rate of development of tension \( (\frac{dp}{dt}) \) and a slight shortening of the time to peak tension (TPT). Since tension develops at a slower rate and for a shorter time than normal, peak developed tension \( (\text{PDT}) \) is reduced, as is the \( \text{force-time integral} \) (FTI), the area under the contraction curve occupied by contraction \text{per se}. In general, these findings are similar to those reported by others for halothane,\(^1\),\(^2\) methoxyflurane,\(^4\) and \( \text{Ethrane} \),\(^5\) and they suggest that the primary effect of anesthetics on contractility is to inhibit the intensity with which the contractility elements generate tension (i.e., anesthetics decrease the intensity of the active state)\(^10\); a less prominent effect is to shorten the duration of the active state.

It is important to recognize that certain aspects of the contraction process are not altered by anesthetics. For example, in our experiments the relaxation phase of contractions was unchanged in appearance and duration. Also, the period of latency between electrical stimulation and the onset of contraction was unaltered. This indicates that these concentrations of general anesthetics do not simply produce a nonspecific depression of cellular functions in general. Their inhibitory effect on contractility, therefore, probably results from a selective action on a specific process concerned
Fig. 3. Calculated linear regression lines showing dose-response relationships between anesthetic concentrations and isometric contraction variables in vitro. The numbers of muscles studied were: diethyl ether, 10; cyclopropane, 9; halothane, 10; methoxyflurane, 4; ethylene, 5. Control values in each muscle were within the following ranges: PDT 3–5 g, dp/dt\textsubscript{max} 15–40 g/sec, FTI 0.25–0.35 g/sec, and TPT 175–200 msec. Bars show the SE for the variables at anesthetic concentrations of 1 MAC; SE's at 2 MAC and 3 MAC were comparable and are not shown. An analysis of variance of the y intercepts at 1 MAC showed that the anesthetics differed in potency (P < 0.01) in their effects on PDT, dp/dt\textsubscript{max}, and FTI (panels A–C) but not in their effects on TPT (panel D).
Fig. 4. Relationship of per cent decreases of PDT (panel A) and FTI (panel B) to per cent decrease in dp/dt_max. Note that changes in these variables are similar for each anaesthetic over a wide range of concentrations.
with the regulation of myocardial contractility. This theme is pursued in another paper in which we present indirect evidence suggesting that this specific process is in fact the release of the membrane-bound calcium involved in excitation-contraction coupling.

The five anesthetics used in these experiments produced qualitatively similar changes in all of the contraction variables analyzed. From this we infer that their actions on contractility probably are identical at the molecular level. Nonetheless, these agents clearly differed quantitatively in both absolute potencies and depressant effects on the heart relative to those on the brain. When administered in vitro to papillary muscles at equieffective concentrations in terms of general anesthesia in vivo (equal MAC's) the order of activity, from most to least depressant, was: Ethane > halothane > methoxyflurane > cyclopropane > diethyl ether. Others have estimated relative activities of series of anesthetics as myocardial depressants both in vitro and in the heart–lung preparation of the dog. Precise comparison of these studies with ours is complicated by the fact that the in vitro experiments were conducted at temperatures of 29 to 32 C and that anesthetic concentrations were expressed as mg/100 ml rather than partial pressures or MAC values. Nonetheless, wherever comparisons can be made, they are in agreement with the order of activity noted above. This suggests that the relative potencies of these anesthetics in the mammalian heart may be similar from species to species and may apply in vivo as well as in vitro.

As a sideline observation, it should be noted that the effects on isometric contractility were not altered in any way by propranolol. From this we conclude that the anesthetics studied do not directly stimulate β-adrenergic receptors in cat papillary muscle nor do they stimulate the release of norepinephrine from adrenergic nerve endings. Low concentrations of halothane have been reported to stimulate weakly the β-adrenergic receptors of rat atria, but this does not occur in cat papillary muscles.

Finally, it is of interest to relate the potencies of anesthetics as depressants of myocardial contractility to their physical properties as volatile lipid-soluble compounds. The appropriate physical constants for each agent are included in table 2. Figure 5A shows a plot of MAC's (potencies in the brain) and EDC's (equieffective concentrations, or potencies in the heart) vs. oil/gas partition coefficients, while figure 5B shows a similar plot of MAC's and EDC's vs. saturated vapor pressures. In figure 5C "vapor pressure at 1 MAC or at EDC" is plotted on the ordinates against saturated vapor pressure on the abscissae. The fact that these variables are related is known as the Ferguson effect and the unit "vapor pressure required to produce anesthesia/saturated vapor pressure" is an index of the thermodynamic activity of an anesthetic. Eger et al. have pointed out that MAC values for a large series of anesthetics correlate better with oil/gas partition coefficients than with other physical constants. Figure 5 shows that in the cat these various functions are related.
by slightly curved lines when experimental values are plotted on a log-log scale. The best correlation is indeed between MAC and oil/gas partition coefficients, but the dominant conclusion one might draw is that our data are compatible with any of these hypotheses. We are intrigued by the fact that correlations between the physical properties of anesthetics and their biological activities seem to apply just as well to the depression of myocardial contractility as to the production of general anesthesia. This suggests that heart muscle (a tissue whose function can be appraised quantitatively in vitro) may be at least as useful a model as the brain for the exploration of the biophysical mechanisms of the actions of anesthetics on excitable cells.

The authors are grateful to Miss Maria Luisa Villarroya and Miss Susan Habler for their technical assistance.

References


---

**Drugs**

**SOTALOL** Methanesulfonanilide hydrochloride (Mead Johnson 1999), a beta blocker, was used in 20 patients with heart disease, eight of whom were in heart failure. Stroke index and left ventricular end-diastolic pressure were unaffected. Sotalol had no effect on the velocity of isotonic shortening (Vmax) in dogs. It appears that sotalol lacks the negative inotropic effects of propranolol and pronethalol. (*Brooks, H., and others: Sotalol-induced Beta Blockade in Cardiac Patients, Circulation 42:09 (July) 1970.*)

**GLUCAGON** The central and peripheral hemodynamic effects of glucagon were studied in 29 patients. Single intravenous doses of 2 or 5 mg increased myocardial contractility, cardiac output, and cardiac performance, as well as lowering pulmonary arterial pressure and pulmonary vascular resistance. Systemic pressures increased and systemic resistance decreased. These results indicate the importance of further study of the value of glucagon as a positive inotropic agent in low-output heart failure. (*Murtagh, J. G., and others: Haemodynamic Effects of Glucagon, Brit. Heart J. 32: 307 (May) 1970.*)