Effects of Halothane Anesthesia Compared with Fentanyl Anesthesia and No Anesthesia during Coronary Ligation in Rats

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The effects of halothane and fentanyl anesthesia on responses to ligation of a coronary artery in chronically prepared rats were compared with responses in conscious animals. A total of 86 rats were used; 24 were ligated under halothane anesthesia, 18 under fentanyl, and 23 were left conscious. Three other groups (each of seven rats) were identically prepared but not ligated. Non-ligated rats were left conscious or anesthetized with halothane or fentanyl. Ligation was performed with the aid of a permanently implanted snare around the left anterior descending coronary artery. The responses to ligation that were measured were: arrhythmias, blood pressure changes, heart rate changes, ECG changes, mortality rates, occluded zone, and infarcted cardiac tissue mass. It was found that 15% of halothane anesthesia starting 30 min before and continuing for 4 h after permanent ligation, had an overall beneficial effect, when compared with controls. Fentanyl (200–1,000 μg/kg, iv) had no overall beneficial effect, compared with conscious controls. Halothane reduced arrhythmias and mortality rates, when compared with controls, while fentanyl did not. Halothane produced lower blood pressures, fewer ECG changes, and lower heart rates than those seen in conscious or fentanyl anesthetized rats. The occluded and infarcted zones produced by ligation were not influenced by the two anesthetics. (Key words: Anesthetics, intravenous: fentanyl. Anesthetics, volatile: halothane. Heart: arrhythmia; coronary occlusion.)

LITTLE IS KNOWN about the effects of anesthetic agents upon the outcome of experimental or clinical myocardial infarction,† despite the relevance of such information to clinical practice. Research is needed to provide both basic scientific and preliminary experimental information as guides to future clinical studies. Therefore, we have concentrated on the influence of anesthetics on the outcome of complete myocardial ischemia and subsequent infarction.

Research in this area is hampered by the lack of suitable models, and lack of adequate concise definitions of the various possible human conditions of myocardial ischemia and infarction to be modelled.2 In the human situation there is undoubtedly a spectrum of conditions varying from slow progressive ischemic heart disease to a sudden abrupt loss of perfusion; we have concentrated on the latter condition by acutely occluding a coronary artery during anesthesia.

Models of ischemia and infarction should include measures of morbidity and mortality rates, as well as measures of arrhythmias, other cardiovascular responses, and infarct size. Although dogs are commonly used for ischemia/infarction experiments, many factors may make them less than ideal. Cost, variability in cardiac anatomy, and difficulties in preparation are some factors. The use of indirect indices of cardiac benefit such as S-T segment elevation, myocardial enzyme release, and changes in regional myocardial blood flow are also less than ideal. Such indices do not directly correspond with morbidity and mortality rates and may not even accurately predict infarct size.3 Furthermore, acute surgical preparation and use of anesthetics contribute further confusing variables.

To overcome some of the above problems, we have developed a chronic conscious rat preparation based upon the work of Selve et al.,4 and our previous studies.5 Other workers6–8 have found rats to be useful in determining drug effects on arrhythmias induced by myocardial ischemia, despite obvious differences in the rat’s cardiovascular system compared to humans, such as in higher heart rate.

In order to determine the effects of anesthetics on responses to myocardial ischemia and infarction, it is necessary to use conscious animals as controls. Our preparation uses chronically prepared animals, thus avoiding the complications of acute surgery and anesthesia. This chronic preparation allows monitoring of responses such as arrhythmias, ECG changes, blood pressure, heart rate, occluded and infarcted cardiac tissue and, most importantly, mortality.

We have tested the effects of halothane and high-dose fentanyl as representatives of inhalational and narcotic anesthetics, respectively, on ligation-induced responses, and compared them with the responses obtained in untreated conscious controls. Each anesthetic agent was used alone to avoid drug interactions.

An initial communication of this work has been given.9 We have previously shown in acutely prepared rats, treated with various drugs, that halothane had beneficial antiarrhythmic effects.10

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Methods

Preparation

Male Wistar rats weighing 250–350 g were prepared under halothane anesthesia, seven to ten days before the experiment, by implanting an occluder around the anterior descending coronary artery and inserting permanent jugular and arterial cannulae and ECG leads. The chest was opened at the fifth intercostal space and the site of ligation of the LAD coronary artery located approximately 3 mm from the aortic root. The occluder snare consisted of a 5-0 polypropylene suture held within a polyethylene guide which was exteriorized in the interscapular region of the neck. The suture was passed through the myocardium so as to make a loop around the artery such that traction between suture and guide (from outside the animal) gave complete ligation of the artery. Insulated stainless steel wires were inserted in limbs and chest as permanently implanted ECG electrodes.

Initially, a permanent catheter was placed in the ventral tail artery and exteriorized at the neck while the rat was under halothane anesthesia one day prior to the experiment. In later animals (44 of the 86), at the time of the thoracotomy, permanent arterial and jugular venous cannulae were inserted in the abdominal aorta and external jugular, respectively, according to the methods of Weeks.‡ After surgery, wounds were infiltrated with 0.5% bupivacaine and animals allowed to recover for six days. Rats appeared to recover completely from the chest surgery within 4–5 days, and those ultimately used for the study were indistinguishable in behavior and health from unoperated controls.

On the day of the experiment, the ECG was reexamined. Three rats with apparent changes from presurgical ECG were excluded from the study. Three other rats with obvious symptomatic respiratory disease also were excluded. In the major experiment, which was performed in two stages, rats were assigned randomly to one of three groups: halothane-anesthetized, fentanyl-anesthetized, or conscious. In a subsidiary control experiment, surgically prepared animals were assigned to three other groups: halothane-anesthetized, fentanyl-anesthetized and conscious rats. The animals in these non-ligation control groups (n = 7) were treated identically to the ligated rats except that the ligation snare was not tightened.

Experimental Procedure

On the day of the experiment, blood pressure and ECG were recorded continuously on a Grass Polygraph for at least 30 min prior to ligation.

‡ Complete details of technique available from J. Weeks, Upjohn Company, Kalamazoo, Michigan, U. S. A.

Conscious animals were kept in a plastic container or home cage, with access to food and water. The animals used early in the study were kept in a plastic container, and intravenous injections were made via a 25-gauge butterfly needle placed in a lateral tail vein. Animals that were used later in the study had a permanent jugular cannula and were kept in their home cage.

Rats that were to receive halothane were induced in a closed box, and once anesthetized, were intubated orally and ventilated at 1 ml/100 g body weight, 60 times/min with halothane in oxygen. Fentanyl-treated animals were restrained while conscious and then anesthetized with 10-µg/kg, iv, increments of fentanyl until (usually a total of 80 µg/kg) they could be intubated for ventilation with oxygen using the same tidal volume and frequency as in the animals given halothane/oxygen. Both anesthetic groups were ventilated by positive pressure respiration. Blood-gas determinations were performed on a sample of animals. Values for PaO2 were 120–125 mmHg, and 36–52 mmHg for PaCO2, with no difference between the mean values for the two anesthetic groups. After intubation, additional fentanyl was given to a total dose of 100 µg/kg prior to ligation. Throughout the experiment, halothane concentrations were adjusted and fentanyl boluses were given to abolish reflex withdrawal from a standardized foot squeeze. This foot squeeze consisted of applying forceps with the same amount of pressure each time to either hind foot once every 15 min. As a result, inspired halothane concentrations varied from 0.7% to 1.0%, while the total fentanyl dose varied from 100 to 1,000 µg/kg over the 4-h observation period (the larger cumulative doses occurred in animals surviving for 4 h).

When blood pressure, ECG, and anesthetic depth were judged to have been stable for at least 15 min, the ligation was tightened in the ligation groups. Stability occurred within 15 min of beginning induction. Conscious rats were treated identically to the other groups except they did not receive an anesthetic and were not intubated or ventilated. Animals in the non-ligated group did not have their occluder tightened.

If a severe ventricular arrhythmia occurred within the 4-h post-ligation observation period, and persisted for longer than 10 s, an attempt was made to convert the arrhythmia to sinus rhythm by repeatedly tapping the rat's chest. Prior exploratory experiments had shown that standardized precordial taps were effective in obtaining reversion of ventricular flutter and fibrillation while technical difficulties made DC defibrillation unreliable. Four hours after ligation, the animals were weaned from the ventilator and returned to their home cages.

If a rat died during the experimental period its heart was excised and perfused via the aorta with Krebs' so-
lution at 30° C and 100 mmHg pressure to clear the heart of blood, then a bolus of 2 ml of cardiac green dye (10 mg/ml) was given via the aortic root. The under-perfused area remained a pale red color, while the perfused tissue appeared green. Both zones were excised and weighed. The weight of the underperfused zone was expressed as a percentage of total ventricular weight, the “ocluded zone.” This determination was always made by an observer who was unaware of the treatment given. In animals that survived 4 h, and following estimation of oclused zone, the heart tissue was sliced and incubated in tetrazolium11 in order to stain viable tissue red and leave infarcted tissue white. After fixation in 10% formaldehyde in saline for two days, the infarct was excised and the weight of infarcted tissue was calculated as a percentage of ventricular weight, the “infarcted zone.” Again, this determination was made “blindly.” Animals that survived were left for 24 h after ligation because our own and other studies12 have shown that infarct size is relatively stable by this time post-ligation in the rat, and that no further mortality occurs after 24 h. The blood pressure and ECG of the surviving rats was recorded at 24 h before the rats were killed by concussion and exsanguination. Hearts were excised rapidly, and the oclused and infarcted zones determined.

Recorded Variables

Heart rate, blood pressure, and ECG were recorded continuously for 30 min before, and for 4 h after ligation with a final reading 24 h post-ligation. From the ECG record, the time to Q-wave (25 μV or more negative deflection preceding R wave) appearance was recorded and the height of the “S-T” segment above the iso-electric line measured. The latter was measured 20 ms after the initial R-wave and was corrected for signal size (RS height) according to the formula: “S-T” corrected = (“S-T” − “S-T” control) × (RS control/RS).

The arrhythmias noted from ECG and blood pressure traces were premature ventricular contractions, ventricular tachycardia, flutter, and fibrillation. Ventricular tachycardia, in its obvious form, gave a rate of at least 500 beats/min, while the ECG showed a lack of sinus rhythm but obvious sharp R-waves. With such tachycardia, the blood pressure fell slightly, if at all. In ventricular flutter the ECG was typically cyclical in appearance with no sharp R-waves. The blood pressure fell to 30–60 mmHg with a very small pulse pressure. In what we designated ventricular fibrillation, either a torsade de pointes13 or true fibrillation pattern was seen on the ECG. This was coupled with a precipitous fall in blood pressure to less than 5 mmHg. Since these three ventricular arrhythmias could not always be distinguished from each other, and tachycardia often degenerated to flutter, and flutter to fibrillation, they were recorded either as ventricular tachycardia (VT) or as ventricular fibrillation (VF). If VF did not spontaneously revert within 10 s, attempts were made to obtain reversal by standardized precordial taps. If 3 min of such resuscitation failed to achieve reversion, the rat’s heart was excised for estimation of oclused zone.

All arrhythmia histories were scored on a 0–8 arrhythmia scoring scale chosen to give a normal (Gaussian) distribution for untreated ligated animals. The value 0 was given for 0–50 PVC with no VT or VF over the observation period (0–30 min or 0–4 h post-ligation); 1 was scored for 50–500 PVC only; 2 for 500 PVC or one episode of spontaneously reversible VT and/or VF; 3 for more than one episode of spontaneously reversible VT and/or VF; 4 for reversible VT and/or VF; 5 for irreversible VT and/or VF episodes lasting less than 60 s; 6 for irreversible VT and/or VF episodes lasting more than 60 s; 7 for fatal VF within 4–15 min; and 8 for fatal VF causing death within 4–15 min. All analyses were made without knowledge of the anesthetic given. Mortality, at 4 and 24 h post-ligation, was recorded.

The null hypothesis tested was that the presence or type of anesthetic agent did not influence the outcome of coronary ligation in the rat. Statistical evaluation was by analysis of variance using computer package ANOVAR and Duncan’s mean test. A chi-square test was used where appropriate. Statistical significance for means by Duncan’s multiple range test, or chi-square for percentages, was taken as $P < 0.05$.

Results

Ligation of the LAD coronary artery could be accomplished within seconds. In conscious rats the R-wave height of the ECG (chest lead) increased up to four or five times by 2 min post-ligation. This change was followed by a change in what we designated the “S-T” segment. ECG changes were accompanied by a fall in systolic and diastolic blood pressure and less predictable changes in heart rate. Ligation-induced arrhythmias occurred in all conscious rats. Arrhythmias were most frequent within the time periods 5–20 min and 1–3 h post-ligation.

In anaesthetized rats ligation also resulted in arrhythmias, the severity of which varied with the anesthetic.

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Table 1. Arrhythmias Produced by Ligation in Halothane and Fentanyl Anesthetized Rats and in Conscious Control Rats

<table>
<thead>
<tr>
<th></th>
<th>Time Post-Ligation</th>
<th>Halothane (H) (n = 24)</th>
<th>Fentanyl (F) (n = 16)</th>
<th>Conscious Control (C) (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia score</td>
<td>30 min</td>
<td>2.3 ± 0.4</td>
<td>4.6 ± 0.6</td>
<td>3.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>2.4 ± 0.4</td>
<td>5.3 ± 0.4</td>
<td>5.2 ± 0.4</td>
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Statistical significance: H < C = F at 30 min and 4 h.

<table>
<thead>
<tr>
<th>Incidence in group of VT/VF (%)</th>
<th>Time Post-Ligation</th>
<th>Halothane (H) (n = 24)</th>
<th>Fentanyl (F) (n = 16)</th>
<th>Conscious Control (C) (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 min</td>
<td>55/21</td>
<td>61/67</td>
<td>61/48</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>55/21</td>
<td>67/63</td>
<td>74/74</td>
</tr>
</tbody>
</table>

Statistical significance: H < C = F for VF at 30 min and 4 h.

<table>
<thead>
<tr>
<th>Incidence in group of irreversible VF (%)</th>
<th>Time Post-Ligation</th>
<th>Halothane (H) (n = 24)</th>
<th>Fentanyl (F) (n = 16)</th>
<th>Conscious Control (C) (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 min</td>
<td>4</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>4</td>
<td>44</td>
<td>44</td>
</tr>
</tbody>
</table>

Statistical significance: H < C = F at 30 min, H < C = F at 4 h.

<table>
<thead>
<tr>
<th>Log_{10} total PVC</th>
<th>Time Post-Ligation</th>
<th>Halothane (H) (n = 24)</th>
<th>Fentanyl (F) (n = 16)</th>
<th>Conscious Control (C) (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 min</td>
<td>1.4 ± 0.2</td>
<td>1.8 ± 0.1</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>1.6 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>2.3 ± 0.2</td>
</tr>
</tbody>
</table>

Statistical significance: H < C at 4 h.

Except for percentages, all values are means ± SEM with n values indicated above. Arrhythmia Score is described in the Methods section. The Arrhythmia Score from time 0 to 30 min post-ligation is given as 30-min score and that from 0–4 h post-ligation as 4 h. For the other indices of arrhythmias, VT refers to ventricular tachycardia and flutter and VF to ventricular fibrillation. Irreversible VF is irreversible ventricular fibrillation leading directly to death. Log_{10}PVC is log_{10} of premature ventricular contractions detected from continuous blood pressure and ECG traces. At the bottom of each section is a summary of statistical significance between groups as given by analysis of variance and Duncan's test or chi-square where appropriate. The symbol, <, indicates that the value to the left is statistically significantly less than that to the right at P < 0.05. The symbol = indicates no statistically significant difference at P < 0.05.

In both time periods (0–30 min and 0–4 h post-ligation) halothane anesthesia was associated with lower arrhythmia scores than occurred in conscious rats. Scores tended to be higher than controls in the fentanyl group. The differences, however, were only statistically significant for halothane. By 4 h the arrhythmia score for halothane was 42% lower than control, and 47% lower than for fentanyl.

Arrhythmia score reflects the occurrence and duration of episodes of both ventricular tachycardia and fibrillation. The incidence of ventricular tachycardia alone in the three groups was not noticeably influenced by either anesthetic. However, the incidence of ventricular fibrillation in the halothane group was statistically lower than its incidence in either the conscious control or fentanyl groups. This difference was most marked with irreversible ventricular fibrillation. For this most serious of all the arrhythmias, the incidence in the halothane group was also statistically significantly lower than that in both the conscious and fentanyl groups. At 4 h post-ligation, the occurrence of irreversible fibrillation in the halothane group was only 8% that of the fentanyl group and 11% of the control group.

The antiarrhythmic effects of halothane were not as well-reflected in the figures for PVC occurrence. By 30 min and 4 h post-ligation the mean number of total PVCs in the halothane group were 17 and 40, respectively. The corresponding figures for the control group were 40 and 200.

The amount of myocardial tissue occluded by ligation (table 2), and the amount ultimately lost as infarct were unchanged by the anesthetic. The infarcted zone as a percentage of occluded zone (zone-at-risk) also was unchanged.

Although the anesthetic agent did not influence the ischemic and infarcted zones, various ECG changes were influenced. The incidence of Q-wave appearance in the halothane group was significantly less than that occurring in the other two groups (table 2). However, the time to appearance of the Q-wave post-ligation did not vary between groups.

Other ECG changes induced by ligation included the very rapid appearance of giant R-waves and "S-T" segment changes as shown in figure 1. While the "S-T" segment is not well-defined in rats, we were able to show marked changes with ligation (fig. 1A). The increase in "S-T" segment developed most rapidly and to the highest level with fentanyl. With halothane, changes developed the slowest and reached a much lower plateau. By 24-h post-ligation changes were the same for the three groups. Another ECG sequel of ligation is the appearance of giant R-waves (up to 5–8X pre-ligation values). Again, this ECG change was more marked with fentanyl (fig. 1B). Representative numerical values from figures 1A and 1B are given in table 2. These values show how...
Table 2. Occluded, Infarcted Zones, and ECG Changes in Halothane- and Fentanyl-anesthetized Rats and in Conscious Control Rats

<table>
<thead>
<tr>
<th></th>
<th>Halothane (n)</th>
<th>Fentanyl (n)</th>
<th>Conscious Control (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occluded zone*</td>
<td>33.0 ± 1.4</td>
<td>31.1 ± 2.5</td>
<td>29.3 ± 2.8</td>
</tr>
<tr>
<td>(as % of total ventricular weight)</td>
<td>(n = 22)</td>
<td>(n = 18)</td>
<td>(n = 22)</td>
</tr>
<tr>
<td>Infarct zone*</td>
<td>23.3 ± 2.6</td>
<td>24.9 ± 3.0</td>
<td>21.3 ± 3.8</td>
</tr>
<tr>
<td>(as % of total ventricular weight)</td>
<td>(n = 20)</td>
<td>(n = 11)</td>
<td>(n = 13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Fentanyl</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG Changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals in group showing Q-wave (as %)†</td>
<td>21</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Time for Q-wave to appear (min)*</td>
<td>49 ± 26</td>
<td>68 ± 15</td>
<td>55 ± 10</td>
</tr>
<tr>
<td>ΔST at 30 min post-ligation (mV)‡</td>
<td>0.52 ± 0.05</td>
<td>0.72 ± 0.05</td>
<td>0.50 ± 0.06</td>
</tr>
<tr>
<td>(n = 21)</td>
<td>(n = 11)</td>
<td>(n = 17)</td>
<td></td>
</tr>
<tr>
<td>R-wave at 30 min post-ligation (mV)$</td>
<td>0.09 ± 0.08</td>
<td>1.06 ± 0.06</td>
<td>0.73 ± 0.07</td>
</tr>
<tr>
<td>ΔST, normalized for changes in R-wave* size, at 30 min post-ligation (mV)</td>
<td>0.36 ± 0.05</td>
<td>0.39 ± 0.04</td>
<td>0.29 ± 0.05</td>
</tr>
</tbody>
</table>

* No statistical differences.
† Statistical significance: H < F = C.
‡ Statistical significance: H = C < F.
§ Statistical significance: C = H < F.

both "S-T" segment elevation and R-wave were statistically significantly larger in the fentanyl group. However, normalizing the "S-T" segment changes for changes in R-wave size resulted in the loss of statistical significance.

Anesthetic influence on blood pressure is shown in figure 2. Fentanyl anesthesia produced significantly higher systolic blood pressures than occurred in conscious control. Consistently, fentanyl systolic pressures were approximately 30 mmHg higher than those seen with halothane. Conscious controls had higher blood pressures than halothane-anesthetized animals. In all three groups, ligation produced a marked, but approximately equal, fall in systolic pressure. Changes in diastolic pressure (fig. 2B) generally paralleled those with systolic pressures, except that a fall in diastolic pressure with ligation did not occur in the fentanyl group. The small pulse pressures recorded (145/115 mmHg for fentanyl, 115/96 mmHg for control and 106/94 mmHg for halothane) were a result of using a small lumen aortic cannula.

The heart rate changes (fig. 2C) were more erratic than those for blood pressure. In general, conscious control animals started with the highest heart rates and these fell 30 beats/min with ligation. In the halothane group, the pre-ligation rate was slightly lower than in the conscious group. It also fell with ligation. Heart rates of the fentanyl group were low before ligation, but rose dramatically afterwards.

Blood pressure and heart rate findings 24 h post-ligation reflected the initial control rates for the different groups, except for the elevated heart rate in the fentanyl group.

The overall mortality figures are given in table 3. By 4 h post-ligation, significantly fewer animals were dead in the halothane group than in the fentanyl-anesthetized or conscious rat groups. In this time period, as tables 1 and 3 show, mortality in the fentanyl-treated and conscious groups was due to irreversible ventricular fibrillation, while three animals in the halothane group died of non-arrhythmic cardiac failure. Part B of table 3 shows accumulated mortality figures for all halothane and control animals examined in our laboratory. In this compilation, the halothane mortality rate was also significantly lower at both 4 and 24 h post-ligation. In the groups (seven animals per group) of animals surgically prepared and subjected to anesthesia but not ligated, there were no episodes of ventricular tachycardia, flutter, or fibrillation in the 4-h observation period. The total PVC in any animal during the 4-h observation period was less than 20. There was also no mortality in any of the non-ligated animals by 4 or 24 h after sham-ligation.

Discussion

A decreased incidence of ventricular arrhythmias, including ventricular fibrillation, was seen after coronary artery ligation during halothane anesthesia as compared with fentanyl anesthesia or consciousness. The decreased mortality rate during halothane anesthesia resulted from the decrease in the incidence of reversible ventricular fibrillation. These differences between anesthetics occurred, despite the use of equi-anesthetic doses, as judged by abolition of responses to a standardized foot squeeze. Both halothane- and fen-
tanyl-treated animals also failed to respond to a variety of other noxious stimuli, but the foot squeeze was taken as a suitably standardized end point. The results for conscious rats lay within the results for the two anesthetics, arguing against a simple effect of the state of anesthesia per se.

In a previous study in acutely prepared anesthetized rats, we also found that halothane anesthesia was associated with lowered mortality and arrhythmia incidence than occurred with meperidine/$\text{N}_2\text{O}$ or pentobarbital anesthesia.\textsuperscript{10} Other workers have reported on the effects of halothane anesthesia in the setting of myocardial ischemia and infarction. In experiments with rats, Kissin et al.\textsuperscript{14} showed that 1% halothane continued for 5 hours after surgery and ligation of a coronary artery had no effect on mortality rate and infarct size when compared with halothane which was discontinued immediately on completion of surgery and ligation. In their study, conscious controls were not used; ECG changes, including arrhythmias, were not reported. In the dog, however, a comparison of 5-h of pentobarbital or halothane anesthetics,\textsuperscript{15} with conscious controls, showed halothane to reduce both the incidence of death from ventricular fibrillation and infarct size (but not the "zone-at-risk"). Bland and Lowenstein\textsuperscript{16} also have shown in dogs that halothane anesthesia lowers S-T segment elevations induced by ischemia. The latter workers did not report effects on mortality rate.

In humans, few controlled comparisons between halothane and narcotic anesthesia have been made. Kistner et al.\textsuperscript{17} showed superiority of various clinical indices of myocardial oxygenation during halothane anesthesia compared with morphine anesthesia.

The reasons for the beneficial actions of halothane we report here are unclear, but they are not a result of

<table>
<thead>
<tr>
<th>Part A</th>
<th>Halothane (n = 24)</th>
<th>Fentanyl (n = 18)</th>
<th>Control (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>By 4-h post-ligation as %(\ast)</td>
<td>16.7</td>
<td>44.4</td>
<td>43.5</td>
</tr>
<tr>
<td>By 24-h post-ligation as %(\ast)</td>
<td>23.2</td>
<td>50</td>
<td>60.9</td>
</tr>
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Part B—Accumulated Mortality for All Control and Halothane Treatment Animals—Includes Data From Different Studies

<table>
<thead>
<tr>
<th></th>
<th>Halothane (n = 24)</th>
<th>Control (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>By 4-h post-ligation as %(\dagger)</td>
<td>16.7</td>
<td>41.2</td>
</tr>
<tr>
<td>By 24-h post-ligation as %(\dagger)</td>
<td>23.2</td>
<td>50.0</td>
</tr>
</tbody>
</table>

\(\ast\) Statistical significance: H < C = F.

\(\dagger\) Statistical significance: H < C.

FIG. 1. Effect of ligation on (A) "S-T" segment and (B) R-wave size in conscious and halothane- or fentanyl-anesthetized rats. The ECG was recorded continuously in three groups of rats. Conscious (●), halothane- (○), and fentanyl-anesthetized (△) rats were subjected to ligation of a coronary artery at time 0. A shows the changes in "S-T" segment (AST) from control values at 10 min prior to ligation. B shows the change in R-wave size before and after ligation. All values are the means ± SEM from 5–24 rats.

limitation of the extent of myocardial infarction as measured by occluded or infarct zones. Halothane produces a direct myocardial depression proportional to the dose.
administered and coupled with this is a decrease in myocardial oxygen demand. A decreased contractile state could be expected to add to the detrimental effects of ligation and possibly precipitate acute cardiac failure. There was some evidence of cardiac failure, not secondary to arrhythmias, in the present study. The greatest ligation-induced fall in blood pressure occurred with halothane, and the three possible cardiac-failure-induced deaths, not associated with arrhythmias, also occurred in this group. Possibly, halothane improved the oxygen balance in the ischemic tissue and so had a beneficial effect although the net effect of halothane upon ischemic tissue within a depressed myocardium is not clear. Bland et al. have shown that halothane improves
ischemic epicardial ECG patterns, and Smith et al.\textsuperscript{21} have shown an increased oxygen supply/demand ratio in ischemic areas of dog hearts during halothane administration. However, the interpretation of results from these and similar studies is contentious.\textsuperscript{22}

The actions of fentanyl were very different from those of halothane. Fentanyl was not beneficial when compared with controls. It worsened R-wave changes in the ECG, and also had a marked effect on the rat’s cardiovascular system compared with halothane. Although equi-anesthetic doses were used, at least in terms of obtundation of responses to a physical stimulus, the two anesthetics had different effects on blood pressure and heart rate. Fentanyl markedly increased both blood pressure, before and after ligation, and heart rate after ligation presumably through activation of the sympathetic system. In clinical practice, a bradycardia is often present at some stage of fentanyl anesthesia. However, clinically observed responses to fentanyl are complicated by concurrent use of other drugs.\textsuperscript{23} The reasons for the higher blood pressure and heart rate with fentanyl anesthesia, as compared with conscious rats, are unknown. If elevations were due to increased sympathetic tone, this could be expected to increase some of the adverse effects of ligation. Increased heart rate and blood pressure in experimental studies with fentanyl have been noted in other species\textsuperscript{24} but the rat may be extra sensitive to fentanyl’s pressor and tachycardia response.

The question remains as to why arrhythmias were less with halothane than in conscious rats. Since the amount of infarcted or occluded tissue produced by ligation was the same in the different groups, ischemic zone and infarct size variations did not explain the variation in arrhythmias between halothane and fentanyl anesthesia and conscious control rats. The decrease in ventricular arrhythmias with halothane was somewhat surprising in view of halothane’s arrhythmogenic action.\textsuperscript{25,26} Blood pressure and heart rate responses alone would not lead one to expect halothane to be beneficial, although some reports have indicated that tachycardia during myocardial ischemia is arrhythmogenic.\textsuperscript{27} In an analysis of results from more than 100 chronic conscious rats prepared and ligated in our laboratory, we have found that arrhythmia incidence is not correlated with heart rate. Comparison of heart rates and arrhythmia incidence do not suggest that, independent of other actions, the different effects of anesthetics on arrhythmias arose from their effect on heart rate. As opposed to the possible arrhythmogenic actions of tachycardia, the increased afterload of hypertension is definitely recognized to be arrhythmogenic.\textsuperscript{28} This is due in part to increased automaticity resulting from increased stretching of Purkinje fibres.\textsuperscript{29} The increased blood pressure with fentanyl indicated a probable increased afterload.

Consideration of our data and comparison of cardiovascular, ECG and tissue loss data may suggest that halothane has important electrophysiologic actions which are antiarrhythmic in the particular setting of ischemia. It has been reported recently that halothane very effectively suppresses the slow channels revealed by high potassium and catecholamines.\textsuperscript{30} Other electrophysiologic actions of halothane may well account for the reduction in ECG changes (including the decrease in arrhythmias) and the subsequent decreased mortality seen with this anesthetic.

Our study suggests that the effects of anesthesia, anesthetic agents, and, particularly, halothane on the outcome of myocardial ischemia are worthy of more intense investigation.

Whether the beneficial effects of halothane were a result of changes induced by halothane in the electrophysiology of ischemic/non-ischemic tissue, in the myocardial oxygen supply/demand ratio, in decreased sympathetic tone, or by a direct antiarrhythmic effect of halothane is now under study.

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References
9. Collins GA, Johnston KM, MacLeod BA, Walker MJA: The effect


