Comparison of Effects of Three Anesthetic Agents on Induction of Ventricular Tachycardia in a Canine Model of Myocardial Infarction

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The effects of three anesthetic agents on the inducibility of ventricular tachycardia by programmed stimulation were investigated in dogs with a surgically induced left ventricular infarct. Endocardial catheter electrodes were placed at the right ventricular apex under general anesthesia at least 2 weeks after infarction, and the dogs were allowed to recover for 24 hours before undergoing programmed stimulation in the conscious state on two occasions 2 hours apart. A protocol of programmed stimulation with up to seven ventricular extrastimuli was used. In 15 animals, ventricular tachycardia was inducible on both occasions with $3.4 \pm 0.4$ (mean $\pm$ SEM; range, 1–5) extrastimuli. Two hours after baseline conscious induction, the dogs were anesthetized with either halothane, pentobarbital, or a fixed combination of fentanyl-droperidol plus nitrous oxide. Halothane prolonged the PR interval from $99 \pm 4$ to $117 \pm 6$ msec ($p = 0.001$) and the ventricular effective refractory period from $140 \pm 4$ to $157 \pm 6$ msec ($p = 0.008$). The ability to induce ventricular tachycardia was abolished in five of 10 animals ($p < 0.05$). In the animals that remained inducible, the cycle length of tachycardia increased from $153 \pm 10$ to $168 \pm 10$ msec ($p = 0.015$), while the number of extrastimuli required was unaltered. Pentobarbital prolonged the PR interval from $104 \pm 6$ to $124 \pm 6$ msec ($p = 0.004$) and the QT, interval from $270 \pm 10$ to $310 \pm 6$ msec ($p = 0.006$). Ventricular tachycardia remained inducible in only six of 10 dogs ($p < 0.05$) with no change in cycle length or the number of extrastimuli required. Ventricular fibrillation was inducible in an additional three dogs with a number of extrastimuli similar to that required to induce ventricular tachycardia before anesthesia. The neuroleptic combination of fentanyl-droperidol plus nitrous oxide caused no change in basic electrocardiographic intervals or refractoriness. Ventricular tachycardia remained inducible in nine of 10 dogs with no significant change in the cycle length or number of extrastimuli required. We conclude that of the three agents, the fentanyl-droperidol combination is the most successful in permitting reproducible induction of ventricular tachycardia by programmed stimulation. Both halothane and pentobarbital suppress the inducibility of ventricular tachycardia. In addition, halothane slows the tachycardia, while pentobarbital promotes the induction of ventricular fibrillation. (Circulation 1988;78:221–226)

Many anesthetic agents are known to have marked effects on cardiac electrophysiology,¹–⁷ and these are usually avoided during clinical electrophysiological studies. However, general anesthesia is necessary for intraoperative mapping during surgery for arrhythmias and is often used during electrophysiological studies on children or exceptionally anxious patients. Several studies of patients undergoing arrhythmia surgery have suggested that general anesthesia decreases the inducibility of ventricular tachycardia (VT).⁸–¹⁰ However, there are no detailed experimental studies of the effects of general anesthetics on electrically inducible VT. In addition, experimental studies of postinfarction arrhythmias in animals are usually performed under general anesthesia, and the particular agents used may have an important bearing on the results obtained.

Therefore, we examined the effect of three major classes of anesthetics using a canine model of
myocardial infarction to determine which agents have the least effect on the induction and characteristics of VT.

Pentobarbital was chosen as a representative barbiturate because it has been used widely in previous experimental studies; furthermore, it has a close structural resemblance to thiopentone, which is commonly used as an induction agent in clinical anesthesia. Halothane is representative of the various halogenated hydrocarbons used for inhalation anesthesia, while fentanyl-droperidol-nitrous oxide is a popular neuroleptanalgesic combination used in clinical practice.

**Materials and Methods**

This study was approved by the Research and Animal Care Committees of Westmead Hospital and conforms with the principles of the American Physiological Society.

Thirty mongrel dogs (14–39 kg) were intubated after administration of thiopentone (20 mg/kg i.v.). Then, anesthesia was maintained with halothane (1–2%) in a 1:2 oxygen-nitrous oxide mixture delivered by a semipern system. Dogs were ventilated via a cuffed endotracheal tube with a Harvard respirator (South Natick, Massachusetts) (15 breaths/min, 15 ml/kg tidal volume). Under aseptic conditions, a limited thoracotomy was performed at the fourth left intercostal space. A bolus of lidocaine (1–2 mg/kg i.v.) was administered; the left anterior descending coronary artery and its first diagonal branch were ligated separately. The thoracotomy wound was closed, residual air was evacuated from the chest, and the third through fifth intercostal nerves were blocked with bupivacaine to provide analgesia after surgery.

Three dogs died suddenly in the first 2 days after surgery, presumably of ventricular fibrillation (VF). The remaining 27 dogs were anesthetized 2–3 weeks later, and a quadripolar electrode catheter (6 French) was positioned at the right ventricular apex via the left external jugular vein. The catheter was tunneled to the nape of the neck and secured within an external pouch sutured to the skin. Twenty-four hours later, conscious dogs underwent programmed electrical stimulation (EPS) on two occasions 2 hours apart. An intracavitary right ventricular electrogram and from one to three surface electrocardiographic leads (1, aVF, and/or V₅) were recorded simultaneously on paper at 100 mm/sec with an ink-jet recorder (Siemens-Elena, Solna, Sweden). A drive train of eight ventricular paced beats (S₁) was delivered at twice-diastolic threshold current intensity by a battery-powered stimulator (model 870, World Precision Instruments, New Haven, Connecticut) with a cycle length of approximately 400 msec. This was followed by a single extrastimulus (S₂) delivered in mid-diastole, the coupling interval of which was decreased in 10-msec steps until ventricular refractoriness was encountered. S₂ was then set 10 msec above the ventricular effective refractory period, and further extrastimuli were added in the same manner as the first until either a sustained ventricular arrhythmia was induced or a maximum of seven extrastimuli was delivered. A ventricular arrhythmia was considered to be sustained if it lasted longer than 10 seconds. In 97% of cases, VT and VF required rapid pacing or DC shock for termination. Extrastimuli were delivered three times at each coupling interval before the interval was shortened. This protocol has advantages over other commonly used stimulation protocols and has been described in detail. One advantage is that there is only one major variable (i.e., number of extrastimuli), while basic pacing cycle length, site of stimulation, and current intensity are constant. VT was defined as an organized, wide complex rhythm with a cycle length of 110 msec or greater.

VT could not be induced in 12 dogs with this protocol. The remaining 15 dogs had reliably inducible VT. This VT was induced at each of two conscious studies 2 hours apart, and these animals were randomly assigned to one of three groups undergoing a further EPS while anesthetized 2 hours later. Anesthetic doses were chosen according to recommendations for clinical anesthesia in dogs. In group A, anesthesia was induced with 4% halothane in oxygen delivered via a face mask; dogs were then intubated and ventilated with 2% halothane in oxygen (10 ml/kg/min) delivered by a precision vaporizer (Fluotec Mark III, Cyprane, Keighley, Yorkshire, England) with a semipern system. In group B, anesthesia was induced with 30 mg/kg pentobarbital administered by slow intravenous injection; dogs were then intubated and ventilated with 100% oxygen. In group C, profound sedation was produced with the fixed combination neuroleptic Innovar-Vet (40 μg fentanyl + 2 mg droperidol/kg; Smith Kline & French Laboratories, Australia), and the animals were easily intubated. The subsequent inhalation of a 1:3 oxygen-nitrous oxide mixture produced a state of light anesthesia and profound analgesia. Atropine, up to 40 μg/kg, was administered to six dogs when the heart rate dropped by more than 20 beats/min before EPS was performed.

Dogs in all three groups were ventilated at a rate of 15 beats/min, with a tidal volume of 15 ml/kg. Thirty-minute arterial blood samples demonstrated that in all groups the pH and PaCO₂ were within normal limits. The PaO₂ was normal in group C; however, it was elevated in groups A and B (as might be expected from the higher inspired oxygen tension in these animals). All anesthetic regimens provided a level of anesthesia sufficient to abolish limb withdrawal in response to a noxious stimulus, and the palpebral reflex was sluggish or absent. Maintenance of this plane of anesthesia was considered "stable anesthesia." Transient changes in various parameters occurred during the induction of anesthesia in groups A and B, presumably because of increased sympathetic activity; therefore, all
measurements were determined after at least 5 minutes of stable anesthesia as described above.

The right ventricular electrode catheters were removed after the third EPS, and the dogs were allowed to recover. Seven dogs were prepared in the same manner and reinvigated on two additional occasions 2 weeks apart; therefore, these dogs were studied three times with a different anesthetic agent each time. One dog was studied on two occasions. Because of the death of some dogs or the inability to keep them for long time periods, seven dogs were studied only once with one anesthetic agent, which brought the number in each group to 10.

In agreement with previous studies from this and other laboratories,14,15 the inducibility of VT during conscious EPS was consistent during 1 day and over the 6–8-week period during which these studies were undertaken. Although VT was reliably inducible on repeat testing, VF was observed at two of the 60 control inductions in this series. This occurred once in each of two dogs, and both animals had VT at five other control inductions. The number of extrastimuli inducing VF was similar to that inducing VT on the other occasions (three vs. four and four vs. five extrastimuli). Every animal had an inducible tachyarrhythmia at each of the control studies.

The influence of different anesthetics on the incidence and ease of induction of VT was compared before (in the conscious state) and after anesthesia. Student’s paired t test was used for evaluating the statistical significance of differences between continuous variables.

VT inducibility was compared with McNemar’s test for correlated proportions.16 Probability (p) values of less than 0.05 were considered to be significant. All values are expressed as mean ± SEM.

**Results**

**Halothane Anesthesia**

Ten dogs were studied in the conscious state and subsequently during halothane anesthesia (group A); the results for these animals are presented in Table 1.

The heart rate, diastolic threshold, and QT interval were all unaltered by halothane anesthesia, while the PR interval was significantly prolonged (p = 0.001). The cycle length of the drive train used during EPS was similar in halothane-anesthetized and conscious animals; however, the ventricular effective refractory period was prolonged over conscious values (p = 0.008).

During halothane anesthesia, sustained VT could not be induced in five animals (p<0.05) despite the use of seven extrastimuli. VT was induced in the remaining five animals; in these animals, the rate of VT was significantly slower than before anesthesia (153 ± 10 before vs. 168 ± 10 msec after anesthesia; p = 0.015; see Figure 1). Before anesthesia, VT was terminated by ventricular pacing or spontaneous reversion in seven of the 10 animals studied; in the remaining three dogs, cardioversion was required to terminate the arrhythmia. In contrast, none of the dogs with inducible VT during halothane anesthesia required cardioversion. Rapid ventricular pacing terminated VT in four dogs, while the remaining dog reverted to sinus rhythm spontaneously after 15 seconds. In the five dogs where VT could be induced in all studies, the same number of extrastimuli were required, irrespective of whether the animals were conscious or anesthetized with halothane (3.3 ± 0.3 vs. 3.4 ± 0.8).

**Pentobarbital Anesthesia**

Ten dogs with inducible VT were studied in the conscious state and subsequently during pentobarbital anesthesia (group B); the results for these

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**TABLE 1. Data Obtained Before and After Induction of Halothane Anesthesia**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Halothane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>139±8</td>
<td>133±5</td>
</tr>
<tr>
<td>PR interval (msec)</td>
<td>99±4</td>
<td>117±6*</td>
</tr>
<tr>
<td>QT interval (msec)</td>
<td>188±6</td>
<td>188±4</td>
</tr>
<tr>
<td>Threshold (mA)</td>
<td>1.2±0.1</td>
<td>1.2±0.1</td>
</tr>
<tr>
<td>Paced cycle length (msec)</td>
<td>366±10</td>
<td>371±7</td>
</tr>
<tr>
<td>Refractory period (msec)</td>
<td>140±4</td>
<td>157±6*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM; n = 10. *Significantly different from conscious control (p<0.05).

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**FIGURE 1. Effect of anesthetic agents on inducibility of ventricular tachycardia (VT).** Panel A: Plot of VT cycle length (mean±SEM, msec) before (C) and during anesthesia with halothane (H), pentobarbital (P), or fentanyl-droperidol-nitrous oxide (F/D/N). Panel B: Histogram of changes in inducibility of ventricular arrhythmias observed with each anesthetic agent. Unshaded areas, percentage of animals in which VT was successfully induced; stippled areas, proportion of dogs in which ventricular fibrillation (VF) was induced; hatched areas, dogs in which no arrhythmia was induced (NI). Note that antiarrhythmic effect of halothane on inducibility of VT was associated with statistically significant increase in VT cycle length when paired data were compared (*p<0.05).
animals are presented in Table 2. During stable anesthesia, the heart rate and diastolic threshold were not significantly different from conscious values, but the PR and QT intervals were both significantly prolonged (p = 0.004 and 0.001, respectively). The QTc interval was also prolonged (270 ± 10 before vs. 310 ± 6 msec after anesthesia; p = 0.006). The drive train cycle length and ventricular effective refractory period were similar in pentobarbital-anesthetized and conscious animals.

During pentobarbital anesthesia, sustained VT was induced in six of the 10 animals (p < 0.05); in these animals, the rate of VT was not significantly different from before anesthesia (159 ± 15 before vs. 165 ± 13 msec after anesthesia). VF was induced in three dogs. VF had never been induced before in two of these animals; the third dog had VF induced in one of six control studies. No arrhythmia was induced in the remaining dog despite the use of seven extrastimuli (Figure 1). There was no difference in the number of extrastimuli required to induce a ventricular tachyarrhythmia (VT or VF) in the nine animals before or after anesthesia (3.6 ± 0.5 before vs. 3.7 ± 0.2 for VT and 3.5 ± 0.6 for VF after anesthesia). Of the six pentobarbital-anesthetized dogs with inducible VT, rapid ventricular pacing terminated the arrhythmia in only two animals, cardioversion being required for the remaining four. Pentobarbital-anesthetized dogs tolerated the cardiovascular consequences of sustained VT poorly and, therefore, required cardioversion more frequently.

Neuroleptanesthesia

Ten dogs with inducible VT were studied in the conscious state and after administration of fentanyl-droperidol-nitrous oxide (group C); the results for these animals are presented in Table 3. Under these anesthetic conditions, the diastolic threshold, PR interval, and QT interval were not significantly different from conscious values. Administration of atropine to six animals may have abolished a change in PR interval resulting from the administration of fentanyl-droperidol.

The drive train cycle length and ventricular effective refractory period were similar before and after the institution of neuroleptanesthesia. With this anesthetic, VT could be induced in nine of the 10 animals studied (p > 0.1; Figure 1), and in these nine dogs, the rate of VT was not significantly different from that before anesthesia (142 ± 8 before vs. 151 ± 10 msec after anesthesia). In the last dog of the 10, nonsustained VT lasting 8 seconds was induced with three extrastimuli; this dog belonged to the subgroup to which atropine was administered. A similar number of extrastimuli were required to induce VT before and after neuroleptanesthesia (3.3 ± 0.3 before vs. 3.1 ± 0.3 after anesthesia). Rapid ventricular pacing successfully terminated the arrhythmia in eight of the nine dogs, and VT reverted spontaneously after 18 seconds in the remaining dog.

Discussion

The ability to reproduce clinical arrhythmias under general anesthesia is vital for detailed intraoperative mapping during VT surgery. Several studies have indicated that electrophysiologically guided surgery is superior to blind resection.17-19 Therefore, inability to produce VT under general anesthesia may lead to reduced efficacy of this type of surgery. Although VT is usually inducible in 80–90% of patients undergoing VT surgery with conventional anesthetic regimens,8-10 This may be due to the anesthetic agents themselves rather than to operative technique, and the results of the present study support this contention. Halothane and pentobarbital suppressed arrhythmias in 40–50% of dogs with reliably inducible VT. In contrast, neuroleptanesthesia caused no significant change in the inducibility or character of VT. The effect of atropine on VT induction during neuroleptanesthesia cannot be determined from the present study, but it is likely to be slight (VT was inducible in five of six dogs receiving atropine compared with all four dogs not receiving atropine). Bertolo and collaborators demonstrated that droperidol used in doses smaller than those used in the present study suppressed early ventricular ectopics and fibrillation after myocardial infarction in cats. However, these animals were studied under pentobarbital anesthesia, and no attempt was made to investigate the effect of droperidol on arrhythmias occurring more than 1 hour after infarction.
Halothane sensitizes the myocardium to catecholamines, and this may predispose to ventricular arrhythmias during the stress of surgery. However, in the present study, halothane was antiarrhythmic in subjects with electrically inducible VT. Other investigators have also found halothane to have antiarrhythmic activity in various settings. MacLeod and associates reported that halothane suppressed early postinfarction VF when compared with fentanyl-anesthetized or conscious rats. Logic et al reported anesthetized nine dogs with halothane 1-3 days after infarction and showed that ventricular ectopic beats were suppressed and idioventricular tachycardia was slowed or terminated by this agent. Halothane has also been shown to suppress induction of atrial and ventricular tachyarrhythmias by programmed stimulation in 33% of dogs.

The present study and others have shown that halothane depresses atrioventricular conduction at the level of the atrioventricular node. This property of halothane has important implications for its use during surgery for supraventricular tachycardia. Because the most common types of supraventricular tachycardia incorporate the atrioventricular node in the reentrant circuit, halothane is likely to inhibit intraoperative arrhythmia induction.

We found that pentobarbital prolonged QT and QTc intervals, without altering ventricular refractoriness, and that it predisposed to induction of VF. QT interval prolongation after induction of anesthesia with thiopental, another barbiturate, has also been observed clinically. This alteration in ventricular repolarization may be analogous to the congenital or drug-induced long QT syndromes and their tendency to result in torsades de pointes, or VF.

Implications

If the data from these experiments in dogs are applicable to humans, it may be wise to avoid halothane and barbiturate anesthetics in patients in whom reproduction of clinical VT, and possibly other arrhythmias, by programmed stimulation is desired. Of the three agents tested, a fentanyl-droperidol-nitrous oxide combination was the best for this purpose. In addition, halothane and barbiturate anesthesia should be avoided in animal experiments requiring the induction or mapping of postinfarction VT.

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**KEY WORDS** • pentobarbital • neuroleptanesthesia • halothane
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