Conscious-state Comparisons of the Effects of Inhalation Anesthetics on Specialized Atrioventricular Conduction Times in Dogs

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The effects of 1.2, 1.7, and 2.3 MAC enflurane (ENF), halothane (HAL), and isoflurane (ISO) on specialized atrioventricular (AV) conduction times were compared with awake (control) in 23 dogs that were chronically instrumented for His bundle studies. Compared with awake, 1.2 MAC ENF and HAL produced 17% and 18% increases in AV nodal conduction time, respectively. There was little added prolongation related to depth of ENF or HAL. ISO did not prolong AV nodal conduction time at 1.2 MAC compared with awake, but it did prolong conduction compared with awake at 1.7 (9%) and 2.3 MAC (15%). All agents produced an approximate 5% increase in His-Purkinje and ventricular conduction times compared with awake, with little additional effect related to depth of anesthesia. In separate experiments in ten of these dogs, anesthetic effects on conduction were determined following combined autonomic blockade with atropine and propranolol. During autonomic blockade, there was no effect of any anesthetic compared with awake, or to increased level of anesthesia, on specialized AV conduction times. The authors conclude that of the major inhalation anesthetics in current clinical use, ISO is least depressant of and ENF and HAL about equally depressant of AV nodal and His-Purkinje conduction times. Furthermore, depression of AV nodal conduction appears to be an indirect rather than direct effect of anesthesia. Finally, most depression of conduction occurs with light anesthesia, with little added depression related to depth of anesthesia over levels likely to be encountered clinically. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: arrhythmias; conduction; electrocardiography. Parasympathetic nervous system: atropine. Sympathetic nervous system: propranolol.)

KNOWLEDGE of anesthetic effects on specialized atrioventricular (AV) conduction is important for the management of patients with heart block and other cardiac rhythm disorders during anesthesia. The catheter His bundle recording technique, introduced in 1968 by Scherlag and associates,1 permits assessment of drug effects on specialized AV conduction times. It has been used for this purpose in dogs for studies of anesthetic effects on specialized AV conduction times.2-7 However, the catheter technique precludes awake, control measurements in dogs, since small movements could dislodge the electrodes, thereby affecting the reproducibility of AV conduction measurements. Thus, heretofore, it has been possible to determine only the effects of increasing anesthetic level on specialized AV conduction times.

In order to assess anesthetic and other drug effects on specialized AV conduction times compared with awake, we developed a technique that permits chronic His bundle recording in conscious dogs.8 The preparation provides reproducible values for AV conduction times for up to a yr, and, hence, a relevant control for the determination of anesthetic effects on specialized AV conduction. We have used this model to determine the effects of enflurane, halothane, and isoflurane on specialized AV conduction times compared with awake.

Methods‡

SURGICAL PREPARATION

The method and validation of methods for the surgical implantation of chronic, cardiac electrophysiologic electrodes in dogs are described elsewhere.8 Briefly, a right thoracotomy was performed under thiopental, halothane, nitrous oxide-oxygen anesthesia. Bipolar, platinum-iridium, ring electrodes were sutured to the epicardial surface of the left and right atrial appendages, the right atrium at its junction with the superior and inferior vena cavae, and the apex of the right ventricle. A unipolar, insulated, platinum-iridium needle electrode was advanced into the interatrial septum from the aortic root for recording the His bundle electrogram (Hiss electrode). The His electrode was referenced to a unipolar ring electrode sutured to the adventitia of the proximal ascending aorta. Wires leading from the electrode pairs were tunneled subcutaneously to a 12-pin connector assembly (Microtech) located between the scapulae.

AV Conduction Measurements

Electrically shielded, 12-strand conduction cable (Microtech) led from the connector assembly to ECG recording amplifiers (Electronics for Medicine/Honeywell

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‡ This research conforms with the standards set forth in the “Guide for Care and Use of Laboratory Animals,” Public Health Services, NIH publication no. 85-23 (Rev. 1985). The animal facilities where this research was conducted are accredited by the American Association for the Accreditation of Laboratory Animal Care.
On 28 testing occasions (ten dogs), arterial pressure was determined with the animal awake and restrained in the standing harness. For this, a 4 Fr Cook™ catheter was inserted percutaneously under local anesthesia (1% lidocaine) into the femoral artery. On other testing occasions, the arterial catheter was placed following induction of anesthesia. On each test occasion, after 15–20 min to allow the animal to become adjusted to the restraining harness, awake (control) measurements for heart rate and AV conduction times were made. Awake testing always preceded testing with anesthesia.

Following awake measurements, anesthesia was induced by mask with the anesthetic agent delivered in oxygen (fractional inspired O₂ concentration [FIO₂] = 1.0). The trachea was then intubated and the dog was mechanically ventilated to keep the end-tidal level of CO₂ (Beckman LB-2™) between 35 and 40 mmHg. For testing (once weekly), animals were equilibrated at end-tidal levels (Beckman LB-2™) of enflurane, halothane, or isoflurane equivalent to 1.2, 1.7, and 2.3 MAC for the dog. The order of anesthetics as well as level administered was randomized. For halothane, levels were 1.0, 1.5, and 2.0% end-tidal for enflurane, 2.5, 3.8, and 5.1% end-tidal, and for isoflurane, 1.7, 2.6, and 3.5% end-tidal. These levels were chosen as representative of light, moderate, and deep levels of anesthesia in the clinical setting. Following 30–45 min for equilibration, measurements of heart rate and conduction intervals were made at each anesthetic level. Heart rate and blood pressure were stable for at least 10 min prior to measurements. Nineteen dogs were tested with halothane, and 17 each were tested with enflurane or isoflurane. Of these, 14 dogs were tested with each anesthetic. Rectal temperature ranged between 36.5 and 38.2°C during anesthetic testing, which lasted (including time for equilibration) less than 3 h.

**Autonomic Blockade**

To assess the direct effects of anesthesia on heart rate and conduction times, in some dogs (halothane: n = 10; enflurane: n = 9; isoflurane: n = 5), atropine and propranolol were used to produce combined vagal and beta-adrenergic blockade. The initial (awake) iv dose of atropine was 0.2 mg/kg followed by repeat doses of 0.05 mg/kg prior to testing at each anesthetic level (approximate 45-min intervals). Propranolol was given in a single iv dose of 0.5 mg/kg prior to awake testing. This schedule was chosen based on heart rate responses following atropine or propranolol observed in pilot experiments. Larger doses produced no further increase (atropine) or decrease (propranolol) in heart rate in conscious or anesthetized dogs. Combined autonomic blockade was later tested in separate experiments performed on six conscious and noninstrumented dogs. Heart rate responses after block-
ers were determined following iv boluses of acetylcholine (10 μg/kg) and isoproterenol (1 μg/kg).

**Statistical Methods**

All data are reported as mean ± SEM. Paired comparisons, both Student’s t test and the Wilcoxon signed-rank test, were used. The results agreed in almost all cases, but in the event of a discrepancy, results were used from Student’s t test when data from ten or more dogs were compared, and the Wilcoxon signed rank test with data from fewer dogs. With the former, one assumes normally distributed data for both samples. With the latter, the significance level is independent of the true sample distribution. In the case of multiple comparisons (between anesthetics, effect of increasing anesthetic level), an appropriate Bonferroni correction was made. The level for statistical significance was $P \leq 0.05$.

**Results**

**Arterial Blood Gas Values, Arterial Pressure**

Arterial blood gas values (pH, $P_{aCO_2}$, $P_{aO_2}$) were within normal limits for all animals and test conditions. In conscious dogs without autonomic blockade, systolic arterial pressure was 165 ± 3 mmHg and diastolic arterial pressure was 70 ± 2 mmHg. All anesthetics produced progressive reductions in systolic and diastolic arterial pressure with increased depth of anesthesia (table 1). Blood pressure reduction with enflurane at the 1.7 and 2.3 MAC levels was greater than with halothane or isoflurane (table 1).

**Anesthetics on Heart Rate and AV Conduction**

Awake and anesthetized values for the heart rate and conduction times are compared in figure 2. For each anesthetic, two comparisons are made: 1) the effect of anesthesia (1.2 MAC vs. awake); 2) the effect of increased level (1.7 or 2.3 vs. 1.2 MAC). Compared with awake, anesthesia did not significantly alter heart rate (halothane suggestive, $P = 0.059$), but did prolong AV nodal (except isoflurane, $P = 0.70$), His-Purkinje, and ventricular conduction times. Heart rate (fig. 2, panel A) increased with increasing level of halothane (1.7 vs. 1.2 MAC) and enflurane (1.7 or 2.3 vs. 1.2 MAC). AV nodal conduction time (fig. 2, panel B) was not further prolonged by increased halothane or enflurane, but was prolonged by increased isoflurane ($P \leq 0.05$, 1.7 or 2.3 vs. 1.2 MAC or awake). All three anesthetics prolonged His-Purkinje (fig. 2, panel C) and ventricular conduction time (fig. 2, panel D) compared with awake. Enflurane produced dose-dependent prolongation of both His-Purkinje and ventricular conduction times while increased level of halothane affected only His-Purkinje conduction time.

Anesthetic effects on conduction times and heart rate are shown as per cent of their respective awake (control) values in figure 3. AV nodal conduction time was most affected by anesthesia with 17% and 18% increases over awake values with 1.2 MAC enflurane and halothane, respectively. There was little further prolongation with increased level of enflurane or halothane. Isoflurane caused a 9% and 12% increase in AV nodal conduction time over awake at the 1.7 and 2.3 MAC levels, respectively. All agents produced a small (approximately 5%) and comparable increase in His-Purkinje and ventricular conduction time over awake at each level of anesthesia.

Fourteen of 23 dogs received all three anesthetics. Data for heart rate and conduction times obtained in this group of animals are shown in table 2. Heart rate with 1.2 MAC halothane was lower than with comparable levels of enflurane or isoflurane ($P < 0.05$). At 1.2 MAC, enflurane and halothane produced more prolongation of AV nodal conduction time than isoflurane, and halothane more than enflurane ($P < 0.05$). At each of the higher MAC levels, there were no differences among the anesthetics for their effect on conduction times.

**Anesthetics and Autonomic Blockade**

Heart rate responses to acetylcholine and isoproterenol in conscious dogs ($n = 6$) blocked with atropine and propranolol are shown in figure 4. The heart rate increase to isoproterenol 60 min following propranolol was 30 ± 9 beats/min, and 60 min later 50 ± 5 beats/min. In
the absence of autonomic blockade, isoproterenol produced an increase in heart rate of $152 \pm 13$ beats/min in these same, awake dogs (separate testing occasion).

Autonomic blockade with atropine and propranolol had no effect on His-Purkinje or ventricular conduction times in awake or anesthetized dogs. Prior to each of the anesthetics, autonomic blockade increased heart rate in awake dogs by 80–100 beats/min (table 3). Heart rate returned to near awake values (without blockers) with 1.2 MAC anesthesia, with no effect of increased depth of anesthesia on heart rate (table 3). AV nodal conduction time was not affected by autonomic blockade in awake dogs. Also, there was no effect of anesthesia or increased level of anesthesia to prolong AV nodal conduction time in blocked dogs, except for a small but significant increase with 2.3 MAC enfurane (table 3).

**Discussion**

Previous reports of the effects of anesthesia on specialized AV conduction times in the spontaneously beating dog heart have lacked a conscious control, so that only the effects of increased anesthetic level were determined.

While the present study provides data for the effects of increased anesthetic level, more importantly, it compares values obtained during anesthesia with those determined in awake dogs.

*Halothane.* In a previous relevant study from this laboratory, 2.0 MAC compared with 1.25 MAC halothane caused no increase in AV nodal conduction time and a 1.5 ms increase in His-Purkinje time. Our present results compare favorably for the effect of increased halothane on AV nodal conduction, but the increase in His-Purkinje
conduction time (2.3 vs. 1.2 MAC) is smaller (0.5 ms). However, we did observe a 2-ms increase in His-Purkinje conduction time for 1.2 MAC halothane versus awake. The difference between the two studies for the effect of increased level of halothane on His-Purkinje conduction time is small. It could reflect a possible overestimation of the halothane effect in our earlier study. In that study, a paper recording technique was used for measuring AV conduction times. Since the recording speed was 200 mm/s, a difference in conduction times of 5 ms would be equal to 1 mm, and differences smaller than 2.5 ms (0.5 mm) probably could not be accurately measured. Consequently, in that study, it is possible that either we could have found no difference or overestimated the difference for the effect of increased halothane on any particular value observed for His-Purkinje conduction time. In the present study, a digital oscilloscope with 1.0 ms resolution was used to calculate AV conduction intervals. The data indicate that over clinically relevant levels, only a small increase in His-Purkinje conduction time would be expected, with most of that due to anesthesia (1.2 MAC vs. awake) and not to increased anesthetic level.

**Enflurane.** The same measurement technique (digital oscilloscope) was used for determining AV conduction times in this and our earlier study with enflurane. The finding of no effect of increased level of enflurane on AV nodal conduction time is in close agreement between the two studies. While we found no effect of increased enflurane (2.0 vs. 1.0 MAC) on His-Purkinje conduction time in the first study, now we find a 1.5 ms increase for 2.3 MAC compared with 1.2 MAC in addition to the 1.5 ms increase for effect of anesthesia (1.2 MAC vs. awake).
We note that in the present study, the increases in AV nodal and His-Purkinje conduction times with anesthesia, and absence of increases related to increased level of anesthesia, appear similar with both halothane and enflurane. What appears most clinically relevant is the observation that most depression of conduction is due to anesthesia and not to increased depth of anesthesia.

*Isoflurane.* Blitt and associates found no effect of increased isoflurane (2.0 or 2.5 vs. 1.25 MAC) on either AV nodal or His-Purkinje conduction time in the spontaneously beating dog heart. They also found rather large standard errors for measured specialized conduction intervals, which they attributed to "marked variability" of the effects of isoflurane on conduction, in contrast to those that had been earlier reported for enflurane or halothane. Another explanation for the variance appears to be the recording paper speed used in study of Blitt et al. (100 mm/s, 10 ms = 1 mm). This could have prevented detection of possible increases in conduction times related to depth of anesthesia. In the present study, it appears that isoflurane (1.2 MAC) does not prolong AV nodal conduction time compared with awake, but does produce 9% (1.7 MAC) and 12% (2.3 MAC) prolongation related to increased anesthetic level. The effect of isoflurane on His-Purkinje and ventricular conduction time appears quite similar to that of enflurane and halothane.

Combined vagal and beta-adrenergic blockade was used to determine whether anesthetic effects on conduction times were direct or dependent on changes in autonomic tone. Most relevant to interpretation of the present data are results with respect to heart rate and AV nodal conduction time (discussed subsequently) because both of these are well known to be influenced by alterations in vagal or sympathetic tone. The absence of significant effects of combined atropine and propranolol on His-Purkinje or ventricular conduction times in awake dogs in this study, as well as no effect of combined blockade to alter anesthetic effects on these variables, support the contention that anesthetic effects to prolong conduction in vivo are not directly mediated.

**Heart Rate.** Heart rate was markedly increased in awake dogs with combined autonomic blockade. The addition of anesthesia (irrespective of anesthetic agent or level) returned heart rate to near awake (without blockers) values. This suggests a direct depressant effect of anesthetics on sinoatrial (SA) nodal function, consistent with their reported effect in the isolated superfused guinea pig heart. However, our autonomic blockade may confound the interpretation for the mechanism of anesthetic effects on heart rate for two reasons: 1) atropine with propranolol in the absence of ganglionic blockade may have caused "excess tachycardia" of anywhere from 25 to 50 beats/min; 2) heart rate responses to isoproterenol at 60 and 120 min (fig. 4) indicate that beta-adrenergic blockade was not complete during anesthetic testing in the present experiments. Other factors to be considered in interpreting the results of present experiments for anesthetic effects on heart rate include: 1) resting heart rates observed in awake dogs; and 2) an expected baroreceptor-mediated increase in heart rate following a decrease in blood pressure with anesthesia. First, our resting rates are somewhat higher than those reported by others (in

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>HR (beats/min)</th>
<th>AH (ms)</th>
<th>HV (ms)</th>
<th>HS (ms)</th>
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<tr>
<td>ENF (1.2)</td>
<td>121 ± 5</td>
<td>93 ± 5</td>
<td>31.4 ± 1.4</td>
<td>90 ± 4</td>
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<td>HAL (1.2)</td>
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<td>100 ± 6*</td>
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<td>90 ± 4</td>
</tr>
<tr>
<td>ISO (1.2)</td>
<td>126 ± 6†</td>
<td>88 ± 5†</td>
<td>30.6 ± 1.4†</td>
<td>90 ± 3</td>
</tr>
<tr>
<td>ENF (1.7)</td>
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<td>95 ± 5</td>
<td>32.4 ± 1.1</td>
<td>91 ± 4</td>
</tr>
<tr>
<td>HAL (1.7)</td>
<td>116 ± 7</td>
<td>97 ± 5</td>
<td>31.5 ± 1.2</td>
<td>90 ± 4</td>
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</tr>
<tr>
<td>ENF (2.3)</td>
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<td>93 ± 4</td>
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<tr>
<td>HAL (2.3)</td>
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<td>98 ± 4</td>
<td>32.0 ± 1.4</td>
<td>91 ± 4</td>
</tr>
<tr>
<td>ISO (2.3)</td>
<td>123 ± 6</td>
<td>98 ± 5</td>
<td>31.4 ± 1.3</td>
<td>92 ± 3</td>
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* P ≤ 0.05 HAL vs. ENF (same level).
† P ≤ 0.05 HAL vs. ISO (same level).
‡ P ≤ 0.05 ISO vs. ENF (same level).

FIG. 4. Heart rate responses to acetylcholine (ACH) and isoproterenol (ISO) in conscious dogs (n = 6) blocked with propranolol (P) and atropine (A). From left to right: CON = control heart rate in absence of blockers; P10, P25 = heart rate 10 and 25 min following P along with responses to ISO at these times; A5, A25 = heart rate 5 and 25 min following A along with responses to ISO at these times; AR1 = first repeat dose of A (60 min following P and 50 min following initial A) along with responses to ACH and ISO at this time; AR2 = second repeat dose of A 1 h later, along with responses to ACH and ISO at this time (*P < 0.05 compared with AR1, or AR2).
ANESTHETICS AND AV CONDUCTION TIMES

TABLE 3. Effect of Autonomic Blockade (B = atropine and propranolol) on Heart Rate and AV Nodal Conduction Time in Dogs Anesthetized with Halothane (HAL), Enflurane (ENF), or Isoflurane (ISO) (Number of dogs shown in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate (beats/min)</th>
<th>AV Nodal Conduction Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAL (10)</td>
<td>ENF (9)</td>
</tr>
<tr>
<td>Awake</td>
<td>121 ± 8</td>
<td>109 ± 5</td>
</tr>
<tr>
<td>Awake + B</td>
<td>201 ± 10*</td>
<td>209 ± 12*</td>
</tr>
<tr>
<td>1.2 MAC + B</td>
<td>126 ± 5†</td>
<td>128 ± 5†</td>
</tr>
<tr>
<td>1.7 MAC + B</td>
<td>125 ± 7</td>
<td>114 ± 3</td>
</tr>
<tr>
<td>2.3 MAC + B</td>
<td>123 ± 5</td>
<td>114 ± 3</td>
</tr>
</tbody>
</table>

* P < 0.05 Awake + B vs. Awake.
† P < 0.05 1.2 MAC + B vs. Awake + B.
‡ P < 0.05 2.3 MAC + B vs. 1.2 MAC + B.

the range of 65–100 beats/min).13–16 This could reflect inadequate conditioning to the laboratory environment, young age (some of our dogs were between 8 months and 1 yr of age), and posture (standing harness compared with lying quietly13–16). Second, while the baroreceptor response may be altered by anesthetics,17–20 one would expect a reduction in blood pressure related to anesthesia or depth of anesthesia15,16 to be countered by an increase in heart rate mediated by a reduction in vagal and increase in sympathetic tone. This would oppose the expected (directly mediated) decrease in heart rate with anesthesia.12

AV Nodal Conduction Time. AV nodal conduction time was unaffected by combined blockade in awake dogs (alone, atropine shortens and propranolol prolongs AV nodal conduction time in conscious dogs8), and there was no effect of anesthesia or increased anesthetic level to prolong conduction during combined blockade. In the absence of blockers, all anesthetics prolonged AV nodal conduction time compared with awake with little added effect (except isoflurane) related to increased level of anesthesia. These observations argue against a direct effect of anesthesia to prolong AV nodal conduction time. Rather, most depression appears mediated by an indirect (autonomic) mechanism. While this could be removal of sympathetic tone and attenuated baroreceptor responsiveness16,20 with anesthesia, the presence of incomplete beta-adrenergic block during anesthetic testing in the present experiments does not permit such speculation with reasonable certainty.

Taken collectively, the present and previous reports2–7 indicate that enflurane and halothane most, and isoflurane least, depress specialized AV conduction times in dogs. Most of the depression appears related to the anesthetic state, and not to increased level of anesthetic per se. These findings may not apply to humans. But if they do, because of the small magnitude of the changes (particularly with His-Purkinje and ventricular conduction times), it is unlikely that any of the anesthetics would be a cause of significant AV conduction block. However, this may not be the case in patients with previously impaired conduction. Of particular concern would be the potential for additive depression of conduction with beta blockers5,8 and calcium-entry blockers.21

Aside from AV conduction block, cardiac arrhythmias may be due to disorders of automaticity or reentrant excitation.22–24 The latter requires unidirectional conduction block and critical changes in refractoriness.25–27 The magnitude of anesthetic effects on specialized AV conduction times noted in the present study appear too small to be related causally to reentrant tachyarrhythmias, although increased conduction time with anesthesia could facilitate reentrant excitation. At least with enflurane6 and halothane,7 the effects of increased anesthesia on the conduction time of premature beats and refractoriness could be causally related to the ability to provoke atrial arrhythmias electrically.7 Additionally, increasing halothane has effects on ventricular conduction and refractoriness that might favor, but have not been causally related to, reentrant ventricular tachyarrhythmias.25 Thus, there is little evidence at present to suggest that any of the modern inhalation agents could be a direct cause for reentrant tachyarrhythmias. However, the depressant effects of anesthetics on AV nodal conduction noted here, along with increased supraventricular refractoriness26 and depression of sinus node automaticity,12 could help to explain the common occurrence of AV junctional rhythm (commonly termed “isorythmic AV dissociation”)26 with anesthesia. However, a cause and effect relationship between any of the anesthetics and AV junctional rhythm requires that they, in addition to increasing AV nodal conduction time and refractoriness, be shown to preserve or enhance automaticity in AV junctional pacemakers. Finally, the present data provide no information as to anesthetics as a cause for automatic tachyarrhythmias.

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References