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# *Halothane, Enflurane and Isoflurane on Abnormal Automaticity and Triggered Rhythmic Activity of Purkinje Fibers from 24-hour-old Infarcted Canine Hearts*

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**The effects of inhalation anesthetics halothane, enflurane, and isoflurane on spontaneous impulse initiation (automaticity) and triggered sustained rhythmic activity were examined in Purkinje fibers derived from normal (n = 38) and 24-h-old infarcted canine hearts (n = 27) to further understanding of their influence on the cellular mechanisms underlying generation of cardiac arrhythmias. Purkinje fibers from normal or infarcted hearts were superfused with modified Krebs' solution (37° C) with or without epinephrine (2 or 15 μM) and equilibrated with a 97% $O_2$–3% $CO_2$ gas mixture (control). Transmembrane action potentials were recorded using conventional microelectrode techniques, and Purkinje fibers were exposed to anesthetic concentrations equivalent to 2.0 MAC. Normal Purkinje fibers were not spontaneously active unless exposed to epinephrine. All anesthetics (enflurane > halothane, isoflurane; $P < 0.05$) increased automaticity of normal Purkinje fibers exposed to either epinephrine concentration. Partially depolarized Purkinje fibers from infarcted hearts were either spontaneously active or were quiescent. For ischemic fibers that beat spontaneously, abnormal automaticity was sustained (duration > 300 s) or periodic (duration < 300 s). Sustained abnormal automaticity was elicited by epinephrine (15 μM) in some quiescent partially depolarized fibers. None of the anesthetics affected the rate of sustained abnormal automaticity, regardless of whether the induction of such automaticity required epinephrine, nor did anesthetics significantly affect the duration of trains of periodic abnormal automaticity. Finally, quiescent, partially depolarized Purkinje fibers were tested for triggered rhythmic activity during pacing at a cycle length of 800 ms. Halothane and enflurane, but not isoflurane, reduced the duration of trains of triggered rhythmic activity as well as increased the number of drive beats to produce such activity. The authors conclude that although halothane, enflurane, and isoflurane increase the automaticity of normal Purkinje fibers from noninfarcted hearts exposed to epinephrine, they do not affect abnormal automaticity of partially depolarized Purkinje fibers from infarcted hearts. Moreover, halothane and enflurane, but not isoflurane, oppose triggered activity in partially depolarized Purkinje fibers from infarcted hearts. (Key words: Anesthetics, volatile: halothane; enflurane; isoflurane. Animal: dog. Heart: abnormal automaticity; arrhythmias; electrophysiology; normal automaticity; Purkinje fibers; myocardial infarction; myocardial ischemia; triggered activity. Sympathetic nervous system, catecholamines: epinephrine.)**

LITTLE IS KNOWN about the effects of available inhalation anesthetics on cellular electrophysiologic mechanisms generating cardiac arrhythmias during the early stages of acute myocardial infarction. Such knowledge may be important for anesthetic management of patients with coronary artery disease, especially those undergoing myocardial revascularization surgery.

The cellular mechanisms producing arrhythmias related to acute myocardial infarction and drug effects thereon have been investigated[1–6] in the 24-h-old canine infarction model designed by Harris.[1] Ventricular arrhythmias in this model are believed to originate in surviving but ischemic or damaged subendocardial Purkinje fibers.[7] Such fibers are variably depolarized and often exhibit spontaneous impulse generation (abnormal automaticity) and triggered activity due to delayed afterdepolarizations.[2,3] In a previous study from this laboratory, it was reported that halothane decreased the rate of spontaneous activity originating in the ischemic region of 24-h-old infarcted canine hearts.[6] Further, in one preparation that was quiescent under control conditions but exhibited triggered sustained rhythmic activity in response to external drive stimuli, halothane abolished the triggered response.[6]

Thus, the present study was designed to investigate the actions of halothane, as well as enflurane and isoflurane, on spontaneous impulse initiation (abnormal automaticity) and triggered rhythmic activity in partially depolarized Purkinje fibers derived from 24-h-old infarcted canine hearts. In addition, anesthetic effects on abnormal automaticity were compared to their effects on automaticity of Purkinje fibers derived from noninfarcted canine hearts.[8]

## Materials and Methods

This research was approved by the Medical College of Wisconsin Animal Care Committee and conforms with

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standards set forth in the Guide for Care and Use of Laboratory Animals.**

Adult mongrel dogs (N = 65) weighing 12–24 kg were used for experiments. Noninfarcted hearts (n = 38) were derived from animals killed during pentobarbital (30 mg/kg) anesthesia. Infarcted preparations were derived from 27 dogs after ligation of the left anterior descending coronary artery during halothane anesthesia. These animals were allowed to recover from surgery overnight and were killed during halothane anesthesia 22–26 h after ligation. The hearts were quickly excised and the anterior false tendon with attached papillary muscle from the left ventricle was removed and immersed in modified Krebs' solution (22° C) equilibrated with 97% $O_2$–3% $CO_2$. This tissue was further dissected to provide a small (less than 1 $cm^2$) preparation with free running strands of Purkinje fibers. In infarcted hearts, Purkinje fibers were obtained from the pale, apical ischemic zone. Preparations from normal or infarcted hearts were transferred to a 2-ml tissue bath, pinned endocardial surface up to the silicone rubber floor, and superfused (4 ml/min) with modified Krebs' solution (37° C) containing no epinephrine or epinephrine (2 or 15 μM) and equilibrated with a 97% $O_2$–3% $CO_2$ gas mixture. The composition of modified Krebs' solution (millimolar) was: NaCl 137, KCl 3.8, $NaHCO_3$ 12, $NaH_2PO_4$ 1.8, $CaCl_2$ 2.5, $MgCl_2$ 0.5, glucose 5.5, and EDTA 0.05, with a *p*H of 7.4.

Anesthetics in the $O_2$–$CO_2$ mixture were introduced to the superfusate reservoir *via* calibrated vaporizers at concentrations equivalent to 2.0 MAC for the dog.[9] Gas concentrations of halothane (1.5%), enflurane (3.5%), or isoflurane (2%) produced measured superfusate concentrations of 0.42 ± 0.02, 0.88 ± 0.05, and 0.53 ± 0.01 mM, respectively. Tissues were exposed to the desired concentration of anesthetic for at least 5 min prior to measurements, and 10 min was allowed for anesthetic washout.

Transmembrane action potentials were recorded using standard microelectrode techniques. The glass microelectrodes (15–30-MΩ resistance) were coupled by Ag–AgCl wire to a preamplifier (World Precision Instruments, New Haven, CT). Action potential signals were recorded on FM tape (AR Vetter Co., Rebersburg, PA) for later data analysis. Drive stimuli for triggered activity or pacing-induced membrane hyperpolarization (described below) were supplied by a digital stimulator (World Precision Instruments). Stimuli were square-wave pulses lasting 2 ms at 1.5–2.0 × threshold through bipolar Ag wire surface electrodes.

Purkinje fibers from normal hearts did not exhibit automaticity unless exposed to epinephrine (2 or 15 μM). A general outline for the experiments performed on infarcted preparations is shown in figure 1. In the absence of epinephrine, the variably depolarized Purkinje fibers from infarcted hearts exhibited either spontaneous abnormal automaticity†† (20 of 27 hearts) or electrical quiescence (7 of 27 hearts). This spontaneous abnormal activity was inherently unstable and often (15 of 20 hearts) remitted to quiescence during the course of experiments, which lasted as long as 5 h. Thus, more than one type of experiment was performed on some of the infarcted preparations. The spontaneous abnormal activity of fibers from infarcted hearts, illustrated in figure 2, was initially classified by the criteria listed in table 1 as either sustained (fig. 2A) or periodic (fig. 2B). Preparations in either category were considered stable and included in the study if they did not change in the type of activity present before, during, and after anesthetic exposure. Preparations from infarcted hearts that initially were quiescent or that subsequently became quiescent over time were tested for induction of triggered activity by application of 1, 2, or as many as 20 electrical stimuli at a cycle length of 800 ms (75 beats per min). Triggered activity (defined as brief rhythmic activity that required prior stimulation for its

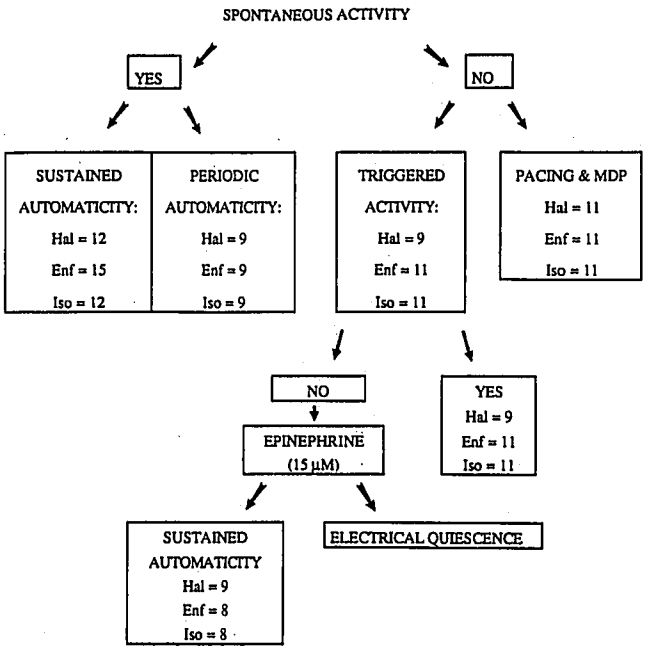


FIG. 1. Outline for experiments performed on Purkinje fiber preparations from infarcted hearts during exposure to halothane (Hal), enflurane (Enf), or isoflurane (Iso). MDP = maximum diastolic potential. See text for details.

** Guide for Care and Use of Laboratory Animals: Public Health Services, NIH Publication no. 85-23 (revised 1985).

†† Spontaneous phase-4 (diastolic) depolarization occuring in partially depolarized fibers is presumably due to different ionic mechanisms than "normal" automaticity occuring at a normal level of maximum distolic potential (MDP) in the same fibers.

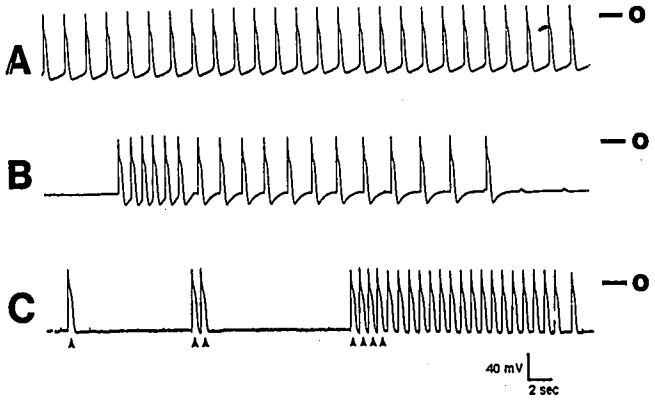


FIG. 2. *A*: Sustained automaticity. *B*: Periodic automaticity. *C*: Triggered activity. (Triangles indicate applied electrical stimuli.)

initiation) is illustrated in fig. 2C. If no triggered activity could be produced, the quiescent fibers were then exposed to epinephrine (15 $\mu$M). This produced sustained abnormal automaticity in 11 of 13 quiescent preparations. In 11 other quiescent partially depolarized fibers, the maximum diastolic potential (MDP) was compared before and during pacing at a cycle length of 800 ms for 20 beats (average MDP for beats 18, 19, and 20 as illustrated in figure 4). These determinations were carried out to test anesthetic effects on pacing-induced (postdrive) membrane hyperpolarization, characteristic of nondepolarized Purkinje fibers.[10] Pacing was also performed in nondepolarized Purkinje fibers from noninfarcted hearts.

Data are shown as mean ± standard error. Control values are those obtained before exposure to a particular anesthetic. Paired and unpaired *t* tests as well as analysis of variance were used for statistical comparisons, with $P < 0.05$ considered statistically significant.

## Results

### Sustained Automaticity of Purkinje Fibers from Normal or Infarcted Hearts

Purkinje fibers from normal hearts were quiescent unless exposed to epinephrine. The spontaneous rate (beats per minute) of "normal" Purkinje fibers exposed to epinephrine 15 $\mu$M (44.5 ± 3.3 bpm) was greater ($P < 0.005$, n = 35) than that of normal fibers exposed to epinephrine 2 $\mu$M (32.9 ± 1.6 beats per min). Partially depolarized Purkinje fibers from infarcted hearts ("abnormal" fibers, n = 25) either exhibited sustained abnormal automaticity (fig. 2A) without the requirement for epinephrine (42.8 ± 3.3 beats per min) or required 15 $\mu$M epinephrine (55.4 ± 5.2 beats per min). The rate in abnormal fibers without epinephrine proved to be significantly greater ($P < 0.005$) than the rate in normal fibers exposed to 2 $\mu$M epinephrine. Although epinephrine significantly increased the intrinsic rate of partially depolarized fibers, the final rate did not differ from the elicited by the same concentration of epinephrine in the normal fibers. These results are summarized in table 2. The MDP of normal Purkinje fibers was greater ($P < 0.05$) than that of partially depolarized fibers. Epinephrine itself had no influence on MDP either in normal or in abnormal Purkinje fibers (table 2).

The effects of halothane (1.5%), enflurane (3.5%), and isoflurane (2%) on sustained automaticity of Purkinje fibers from normal and infarcted hearts are compared in table 3. Automaticity in normal Purkinje fibers exposed to epinephrine (2 or 15 $\mu$M) was augmented by each of the anesthetics compared to their respective controls (table 3). The increase in automaticity with enflurane, however, was greater than that with halothane or isoflurane for both epinephrine concentrations ($P < 0.05$, table 3). In contrast, sustained automaticity of partially depolarized or abnormal Purkinje fibers was not significantly altered by exposure to any of the anesthetics, regardless of whether such automaticity required epinephrine for its expression.

### Periodic Automaticity of Purkinje Fibers from Infarcted Hearts

Brief periods of abnormal automaticity, lasting less than 300 s and with electrical quiescence between periods, was characteristic behavior at one time or another of many preparations from infarcted hearts (fig. 2B). Such periodic automaticity did not require epinephrine for its expression, nor was it dependent on prior stimulated beats as was triggered activity (see below). The average duration of trains of beats during periodic automaticity before and after exposure to anesthetic was compared to control values. There was considerable variance in the duration of trains both before and after anesthetics. Anesthetics had no significant effects on the duration of trains of periodic automaticity (n = 9 for each anesthetic). Because there was also considerable beat-to-beat variation in cycle length of periodic automaticity (table 1), the average rate for such automaticity was not determined.

TABLE 1. Comparison of Sustained with Periodic Abnormal Automaticity in Purkinje Fibers from Infarcted Hearts

| Sustained | Periodic |
|---|---|
| 1. Long–short cycle length variation < 50 ms | 1. Long–short cycle length variation > 50 ms |
| 2. Trains of beats > 300 s | 2. Trains of beats < 300 s |
| 3. Overdrive-suppressed by 30 s of pacing at cycle length = 400 ms | 3. Not suppressed by 30 s of pacing at cycle length = 400 ms |

TABLE 2. Comparison of Sustained Automaticity (rate) and Maximum Diastolic Potential of Purkinje Fibers from Normal and Infarcted Hearts

| | Normal (n = 35) | | Infarcted (n = 25) | |
|---|---|---|---|---|
| | 2 μM EPI | 15 μM EPI | 0 μM EPI | 15 μM EPI |
| Rate (beats per min) | 32.9 ± 1.6 | 44.5 ± 3.3* | 42.8 ± 3.3* | 55.4 ± 5.2† |
| MDP (mV) | 85.3 ± 0.8 | 87.6 ± 1.5 | 78.2 ± 1.1‡ | 81.0 ± 2.9§ |

Values are means ± SE.
EPI = epinephrine; MDP = maximum diastolic potential.
* $P < 0.005$ *versus* 2 μM.
† $P < 0.05$ *versus* 0 μM.
‡ $P < 0.001$ *versus* 2 μM.
§ $P < 0.05$ *versus* 15 μM normal.

### TRIGGERED ACTIVITY IN PURKINJE FIBERS FROM INFARCTED HEARTS

Triggered rhythmic activity was sought in quiescent Purkinje fibers from infarcted hearts by providing up to 20 consecutive drive beats at a cycle length of 800 ms (fig. 2C). The duration (in seconds) of triggered activity following the last drive beat, the number of drive beats required to produce triggered activity, and normalized "severity" scores (duration of trains per number of drive beats) are shown in table 4 for each anesthetic, as well as their respective controls. Halothane (n = 9) and enflurane (n = 11), but not isoflurane (n = 11), reduced the duration of trains of triggered rhythmic activity and increased the number of drive beats required to trigger rhythmic activity. However, there was considerable variance in the duration of trains in controls. In addition, halothane and enflurane, but not isoflurane, reduced normalized severity scores. The effects of halothane and enflurane to oppose triggered activity were not significantly different from one another. Representative tracings for the effect of each anesthetic on triggered activity are shown in figure 3.

### MAXIMUM DIASTOLIC POTENTIAL IN DRIVEN PURKINJE FIBERS FROM NORMAL OR INFARCTED HEARTS

The effect of pacing (20 beats at a cycle length of 800 ms) on postdrive MDP was tested in quiescent Purkinje fibers from normal (n = 13) or infarcted (n = 11) hearts. The effect of such pacing to increase (hyperpolarize) MDP in a normal Purkinje fiber under control conditions is shown in figure 4A. Anesthetic effects on postdrive hyperpolarization of Purkinje fibers from normal or infarcted hearts are shown in table 5. None of the three anesthetics tested opposed the effect of pacing to increase MDP of Purkinje fibers from normal or infarcted hearts. Finally, the pacing-induced increase in MDP was greater in normal than in abnormal Purkinje fibers for all test conditions.

## Discussion

All volatile anesthetics studied, especially enflurane, increased the spontaneous discharge rate (automaticity) of Purkinje fibers derived from noninfarcted canine hearts. Although manifestation of such automaticity required epinephrine (2 μM), it would still be viewed as normal since Purkinje fibers were not partially depolarized as a result of the effects of disease or drugs.[11] In contrast, sustained or periodic automaticity in partially depolarized Purkinje fibers from 24-h-old infarcted hearts, which sometimes required epinephrine, was not affected by halothane, enflurane, or isoflurane. Such sustained or periodic automaticity, since it occurred in partially depolarized fibers, would be considered abnormal.[11] Thus, any of the available potent inhalation anesthetics might be expected to enhance normal but have no effect on ab-

TABLE 3. Effects of Anesthetics on Sustained Automaticity of Purkinje Fibers from Normal and Infarcted Hearts

| | Normal | | Infarcted | |
|---|---|---|---|---|
| Rate (beats per min) | 2 μM EPI | 15 μM EPI | 0 μM EPI | 15 μM EPI |
| Control | 32.9 ± 2.8 (23) | 43.2 ± 5.9 (11) | 45.4 ± 6.7 (12) | 53.7 ± 7.6 (9) |
| 1.5% Halothane | 36.6 ± 2.6* (23) | 47.2 ± 6.0* (11) | 46.8 ± 6.9 (12) | 56.8 ± 8.0 (9) |
| Control | 33.5 ± 2.7 (24) | 46.0 ± 5.7 (13) | 41.3 ± 5.2 (15) | 56.1 ± 9.3 (8) |
| 3.5% Enflurane | 45.7 ± 3.1†‡ (24) | 55.8 ± 6.2†‡ (13) | 45.5 ± 5.5 (15) | 60.4 ± 10.6 (8) |
| Control | 32.4 ± 2.8 (23) | 44.1 ± 6.3 (11) | 42.0 ± 5.8 (12) | 56.8 ± 11.4 (8) |
| 2% Isoflurane | 35.1 ± 2.8* (23) | 46.7 ± 6.3* (11) | 42.8 ± 5.8 (12) | 57.4 ± 13.1 (8) |

EPI = epinephrine.
Values are means ± SE. The numbers in parentheses indicate the number of experiments performed.
* $P < 0.02$ *versus* control.
† $P < 0.001$ *versus* control.
‡ $P < 0.05$ *versus* halothane and isoflurane.

TABLE 4. Effects of Anesthetics on Triggered Activity in Purkinje Fibers from Infarcted Hearts

| | Duration of Trains (s) | Number of Beats | Duration of Trains/ Number of Beats |
|---|---|---|---|
| Control | 27.77 ± 6.79 (9) | 4.70 ± 1.42 (9) | 12.38 ± 3.19 (9) |
| 1.5% Halothane | 4.08 ± 2.52* (9) | 11.52 ± 1.99† (9) | 1.64 ± 1.07* (9) |
| Control | 33.25 ± 7.32 (11) | 4.62 ± 0.83 (11) | 14.57 ± 3.50 (11) |
| 3.5% Enflurane | 7.32 ± 4.91† (11) | 14.18 ± 1.25† (11) | 1.35 ± 0.95† (11) |
| Control | 19.32 ± 5.19 (11) | 5.50 ± 1.46 (11) | 9.88 ± 2.95 (11) |
| 2% Isoflurane | 15.50 ± 6.13 (11) | 7.32 ± 2.09 (11) | 8.15 ± 3.12 (11) |

Values are means ± SE.
* $P < 0.02$ *versus* control.
† $P < 0.005$ *versus* control.

normal automaticity of Purkinje fibers, at least under the present experimental conditions. In addition, in some quiescent but partially depolarized fibers from infarcted hearts, it was possible to induce triggered rhythmic activity following electrically stimulated beats. Halothane and enflurane, but not isoflurane, increased the number of stimulated beats required to induce triggered rhythmic activity and reduced the duration of trains of such activity.

We have previously reported the effects of halothane, enflurane, and isoflurane on normal automaticity and recovery following overdrive suppression of such automaticity in Purkinje fibers from noninfarcted hearts.[8] As noted in that study,[8] all anesthetics but especially enflurane increased the rate of normal automaticity of Purkinje fibers exposed to epinephrine. During exposure to epinephrine (2 or 15 $\mu$M), anesthetic effects on recovery of automaticity following overdrive suppression were tested during 30 or 60 s of pacing at cycle lengths equivalent to 75 (800 ms), 120 (500 ms) or 150 (400 ms) beats/min.[8] Recovery times were most shortened by enflurane and less so by halothane but were not significantly altered by isoflurane. These findings for enflurane were interpreted as consistent with its reported effect to inhibit postoverdrive membrane hyperpolarization; this effect could reflect enflurane-produced inhibition of the $Na^+$-$K^+$ exchange pump.[10] In the present experiments, we did not test anesthetic effects on postoverdrive recovery of automaticity but examined their effects on postdrive membrane hyperpolarization. This was done in Purkinje fibers from normal (normal fibers) and infarcted hearts (abnormal fibers) by comparing MDP before and during the 18th, 19th, and 20th (averaged) drive beats at a cycle length of 800 ms. Purkinje fibers were not exposed to epinephrine during these experiments. The hyperpolarizing effect of pacing was different in normal and abnormal fibers, *i.e.*, produced greater increase in the MDP of normal compared to that of abnormal fibers. Possibly, this might be explained by greater dependence of normal Purkinje fibers on the influx of $Na^+$ for generation of their action potentials than partially depolarized Purkinje fibers from infarcted hearts.[12] In partially depolarized fibers, more $Na^+$ channels are inactivated and less $Na^+$ ac-

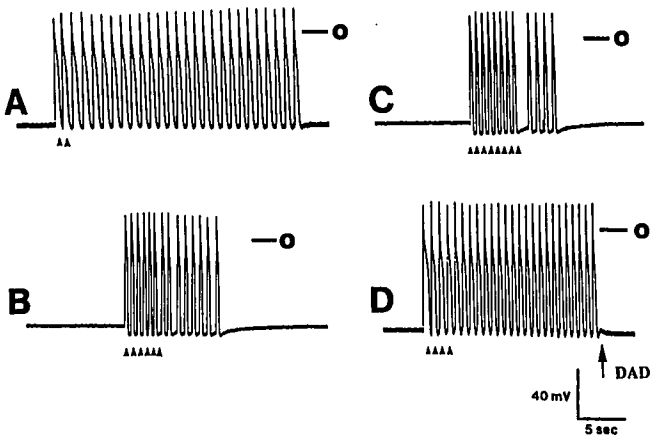


FIG. 3. Representative tracings from experiments for the effects of anesthetics on triggered rhythmic activity. (Triangles represent applied electrical stimuli). *A* (control): Rhythmic activity triggered by two driven beats (arrows). *B* (1.5% halothane): Rhythmic activity triggered by six driven beats. *C* (3.5% enflurane): Triggered rhythmic activity requires eight driven beats. *D* (2% isoflurane): Triggered activity requiring four driven beats and followed by a delayed afterdepolarization (DAD) at the point indicated by the arrow.

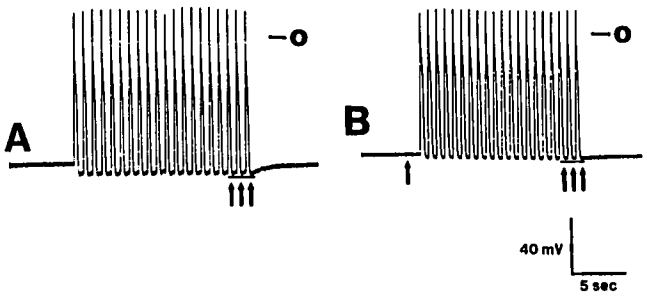


FIG. 4. Effect of pacing on postdrive maximum diastolic potential (MDP) in representative "normal" (*A*) and infarcted (*B*) Purkinje fibers under control conditions. MDP before the first of a series of 20 drive beats (cycle length 800 ms) was 89 mV for normal and 84 mV for infarcted fibers. The average MDP for drive beats 18, 19, and 20 for the normal fiber was 99 mV compared to 88 mV for the infarcted fiber.

TABLE 5. Anesthetic Effects on Pacing-induced Changes in Maximum Diastolic Potential of Purkinje Fibers from Normal and Infarcted Hearts

| | Normal (n = 13) | | | Infarcted (n = 11) | | |
|---|---|---|---|---|---|---|
| MDP (mV) | Before Stimulation | Duration Stimulation | Differences | Before Stimulation | During Stimulation | Differences |
| Control | 81.1 ± 1.0 | 89.2 ± 1.0* | 8.23 ± 0.55 | 77.2 ± 1.4 | 80.1 ± 1.0* | 3.00 ± 0.76† |
| 1.5% Halothane | 80.4 ± 1.1 | 88.2 ± 1.4* | 7.85 ± 0.52 | 77.6 ± 1.2 | 80.3 ± 0.8* | 2.64 ± 0.64† |
| Control | 79.5 ± 1.0 | 87.8 ± 1.3* | 8.42 ± 0.65 | 79.3 ± 1.3 | 8.16 ± 1.4* | 2.00 ± 0.35† |
| 3.5% Enflurane | 77.9 ± 1.3 | 85.6 ± 1.3* | 8.23 ± 0.68 | 79.2 ± 1.4 | 81.8 ± 1.3* | 2.45 ± 0.39† |
| Control | 80.4 ± 1.0 | 88.8 ± 1.0* | 7.69 ± 0.54 | 79.3 ± 1.3 | 81.4 ± 1.3* | 2.36 ± 0.27† |
| 2% Isoflurane | 79.8 ± 1.3 | 88.1 ± 1.5* | 7.46 ± 0.61 | 77.3 ± 1.4 | 79.7 ± 1.6* | 2.64 ± 0.34† |

Maximum diastolic potential (MDP) before stimulation compared to average MDP for drive beats 18, 19, and 20 (during stimulation) and differences between these two.

* $P < 0.005$ *versus* before stimulation.
† $P < 0.001$ *versus* normal differences.

cumulates in the cells during pacing. This might lead to a reduced $Na^+$-$K^+$ exchange as compared to normal fibers and to a smaller hyperpolarization during the pacing protocol.

No anesthetic altered the effect of pacing on postdrive hyperpolarization in Purkinje fibers from normal or infarcted hearts. Although Pratila *et al.*[10] observed that enflurane caused inhibition of postdrive hyperpolarization, that study used higher concentrations, more prolonged pacing, and at a more rapid rate than in the present case. Had we tested anesthetic effects on postdrive hyperpolarization during more prolonged and faster pacing, with or without epinephrine, it is possible that we could have detected differences for anesthetic effects on postdrive hyperpolarization. In turn, possible inhibition of postdrive hyperpolarization by enflurane[10] could, in part, explain its more pronounced effect to increase automaticity of normal Purkinje fibers compared to halothane or isoflurane. Finally, our failure to demonstrate anesthetic effects on postdrive hyperpolarization on abnormal Purkinje fibers from infarcted hearts may explain in part the lack of anesthetic effect on the rate of automaticity in such fibers. Namely, the failure appreciably to alter membrane potential of automatic fibers following a period of drive beats, and assuming that the rate of diastolic (phase-4) depolarization and threshold potential remained constant, should not alter the rate of automaticity.[11]

The ionic basis for abnormal forms of automaticity in partially depolarized Purkinje fibers from infarcted hearts has not been established. Multiple factors could contribute to diastolic sarcolemmal membrane electrical instability responsible for phase-4 depolarization in partially depolarized Purkinje fibers. Phase-4 depolarization in partially depolarized Purkinje fibers must result from an increase in net inward current and/or a reduction in outward movement of positive charges.[11,13] For example, phase-4 depolarization in partially depolarized Purkinje fibers (abnormal automaticity) might be explained as follows. Outward movement of $Na^+$ and $Ca^{2+}$ would be decreased by ischemia-induced or other inhibition of the energy (adenosine triphosphate)-dependent $Na^+$-$K^+$ pump and sarcolemmal $Ca^{2+}$–adenosine triphosphatase. Increased intracellular $Ca^{2+}$ from the $Ca^{2+}$–adenosine triphosphatase inhibition would lead to augmented $Ca^{2+}$-$Na^+$ exchange (three extracellular $Na^+$ enter for one intracellular $Ca^{2+}$ extruded), further enhancing phase-4 depolarization. While augmented influx of $Ca^{2+}$ could also contribute to phase-4 depolarization, anesthetics would not be expected to increase such influx,[14] and neither should ischemia-induced membrane depolarization do so at membrane potentials more negative than −70 mV. If anything, potent inhalation anesthetics should inhibit $Ca^{2+}$ influx[14] and oppose any spontaneous membrane depolarization due to this cause. It is also possible that decreased $K^+$ conductance in partially depolarized fibers would contribute to phase-4 depolarization, since there would be less $K^+$ efflux during repolarization (phase 3). Thus, in partially depolarized Purkinje fibers, even without augmented $Ca^{2+}$ influx, we are left with a net influx of positive charges during phase 4 that could produce spontaneous depolarization, and sustained or nonsustained abnormal automaticity if this process was repetitive.

Since anesthetics are not known to interfere specifically with any of the above-outlined processes, this may account for the lack of observed effects of any of the anesthetics on abnormal automaticity in this study. This might not be the case, however, if automaticity occurred in fibers with MDPs less negative than −70 mV. In that case, anesthetic inhibition of $Ca^{2+}$ influx[14] could contribute to a reduction in the rate of phase-4 depolarization. The magnitude of this reduction would depend on the level of MDP in a particular partially depolarized (< −70 mV) Purkinje fiber. This is because $Ca^{2+}$ channels exhibit voltage-dependent gating characteristics,[15] so that the magnitude of $Ca^{2+}$ influx will vary with changes in MDP less negative than −70 mV. For instance, inactivation of $Ca^{2+}$ channels will be evident at more depolarized membrane potentials, resulting in fewer available $Ca^{2+}$ channels. That

halothane might reduce the rate of abnormal automaticity in Purkinje fibers with MDPs below −70 mV is suggested by previous work from this laboratory.[6]

Halothane and enflurane, but not isoflurane, opposed the induction of triggered rhythmic activity in quiescent but partially depolarized Purkinje fibers from infarcted hearts. Such activity results from delayed afterdepolarizations,[6,11,16] which are attributed to intracellular $Ca^{2+}$ overload.[16] Elevated intracellular $Ca^{2+}$, in turn, initiates 3:1 $Na^+$–$Ca^{2+}$ exchange (described above), which results in a net inward current termed the transient inward current.[17] The latter current is likely responsible for delayed afterdepolarizations. If these reach threshold potential, they can be responsible for triggered rhythmic activity.[11,16] The inhalational anesthetic reduction of transient inward current is likely due to the effect of volatile anesthetics decreasing the sarcoplasmic reticulum store of $Ca^{2+}$, an effect achieved by inhibition of $Ca^{2+}$ efflux,[11] decreased $Ca^{2+}$ release, and/or depletion of the intracellular sarcoplasmic reticulum $Ca^{2+}$ store.[14] The failure of isoflurane to oppose triggered activity in our experiments may be due to less inhibition by isoflurane of $Ca^{2+}$ release from the sarcoplasmic reticulum.[18,19] Finally, the effect of halothane to oppose triggered activity in Purkinje fibers from infarcted hearts is similar to its effect on ouabain-induced delayed afterdepolarizations and triggered activity in Purkinje fibers,[20] as well consistent with earlier observations from this laboratory in Purkinje fibers derived from infarcted hearts.[6]

Due to possible species differences and unknown effects of autonomic and other compensatory mechanisms, our findings for the effect of the available potent inhalation anesthetics must be extrapolated with caution to clinical anesthesia. They do, however, suggest that these inhalation anesthetics would have little effect to alter the rate of ventricular escape rhythms in patients with sinus node dysfunction or atrioventricular heart block. In fact, they might cause a small increase in the rate of escape rhythms. With ventricular arrhythmias due to abnormal automaticity or triggered activity in patients with acute myocardial infarction, anesthetics could have variable effects. The rate of ventricular arrhythmias due to abnormal automaticity should be little affected by any of the anesthetics, especially if surviving Purkinje fibers, responsible for such arrhythmias, were not severely depolarized (MDP > −70 mV). Although this was not the case in our study, if fibers were severely depolarized, then at least halothane might decrease the rate of automaticity[6] due to inhibition of $Ca^{2+}$ influx.[14] Finally, ventricular arrhythmias due to triggered rhythmic activity should be opposed by halothane and enflurane but little affected by isoflurane.

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