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Effects of Halothane and Enflurane on Ventricular Conduction, Refractoriness, and Wavelength

A Concentration–Response Study in Isolated Hearts

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Background: **Effects of halothane and enflurane on ventricular conduction, anisotropy, duration and dispersion of refractory periods, and wavelengths were studied, and putative antiarrhythmic or arrhythmogenic properties on ventricles were discussed.**

Methods: **High-resolution epicardial mapping system was used to study the effects of 1, 3, and 5 vol% halothane and enflurane in 30 isolated rabbit hearts. Ten hearts were kept intact to study the effects on spontaneous sinus cycle length (RR interval), perfusion pressure, and the occurrence of spontaneous dysrhythmias. In 20 other hearts, a thin epicardial layer was obtained (frozen hearts) to study ventricular conduction velocity, ventricular effective refractory period (VERP in four sites) and wavelengths.**

Results: **Halothane induced a concentration-dependent lengthening of RR interval, whereas enflurane did not. Both agents slowed longitudinal and transverse ventricular conduction velocity with no anisotropic change. Ventricular effective refractory period was prolonged at 1 vol% and was shortened at higher concentrations, with no significant increase in dispersion. Ventricular longitudinal and transverse wavelengths decreased in a concentration-dependent manner. Although changes in wavelengths could express proarrhythmic effects of volatile anesthetics, no arrhythmia occurred in spontaneously beating hearts or in frozen hearts.**

Conclusions: **The ventricular electrophysiologic effects of halothane and enflurane were slight, suggesting that both agents are unable *per se* to induce functional conduction block and therefore reentrant ventricular arrhythmias. (Key words: Cardiac electrophysiology; epicardial mapping; isolated heart; volatile anesthetics.)**

HALOTHANE and enflurane have anti- and prodysrhythmic effects at supraventricular and ventricular levels. Although arrhythmias induced or facilitated by halothane and enflurane are thought to be reentrant,[1] this has never been directly shown. Mechanisms for reentry include changes in conduction and refractoriness, resulting in a shortening of the wavelength[2–4] and increase in spatial dispersion of repolarization.[5,6] Volatile anesthetics affect conduction and refractoriness *via* the modulation of various ionic currents flowing through the myocardial cell membrane.[1] In addition, volatile anesthetics alter the cell-to-cell conduction through gap junctions.[7,8] Using epicardial mapping in anisotropic rabbit ventricles, Brugada *et al.*[9] showed that heptanol, which also depresses the gap junction conduction, slows the transverse more than the longitudinal conduction, increasing the anisotropic ratio. These effects were dose-dependent, and conduction blocks occurred in the transverse direction. A similar pattern of conduction alteration could be expected with volatile anesthetics.

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Thus, halothane and enflurane could promote transverse conduction blocks and therefore ventricular anisotropic reentrant arrhythmias. Because this hypothesis has never been addressed in whole isolated hearts, the first aim of the study was to specify, in isolated rabbit hearts, the effects of increasing concentrations of halothane and enflurane on longitudinal and transverse ventricular conduction velocities and on the anisotropic ratio. Moreover, the use–dependency and the occurrence of spontaneous or inducible ventricular arrhythmias were also studied.

The prolongation of repolarization and especially the increased dispersion of refractoriness are associated with a vulnerability to reentrant arrhythmias.[6,10] Although halothane depresses potassium currents,[11] data are lacking concerning effects of halothane and enflurane on dispersion of repolarization. Therefore, the second aim of the study was to investigate the effects of both agents on the duration and spatial dispersion of ventricular effective refractory period (VERP). Finally, because the wavelength (defined as the product of conduction velocity and VERP) is a reliable index of arrhythmogenicity of pharmacologic agents,[2,4] effects of halothane and enflurane on ventricular wavelengths also were analyzed.

Materials and Methods

Heart Preparation

The principles for the care and treatment of experimental animals complied with the national guidelines of the French Ministry of Agriculture, Paris, France. Thirty New Zealand rabbits, weighing 2.4–3.2 kg, were used in this study. After anesthesia with ketamine (35 mg/kg intramuscular), the trachea was intubated and the lungs were mechanically ventilated with 100% O_2 (Servo Ventilator 900 C; Siemens-Elema, Sweden). The thorax was surgically opened by a midsternal incision. The aorta and the heart were exposed and, after anticoagulation with heparin (1,000 IU), they were rapidly removed and placed in cold perfusion fluid (10°C). The aorta was cannulated and the heart was connected to a Langendorff perfusion system using Tyrode solution. The coronary arteries were perfused with a constant flow (Watson-Marlow 101U pump; Falmouth Cornwall, UK) initially adjusted to obtain a pressure of 70 ± 10 mmHg (Gould P23 transducer; Oxnard, CA; CGR monitor; St-Cloud, France). The millimolar composition of the Tyrode solution was: NaCl: 130 mM; $NaHCO_3$: 20.1 mM; KCl: 4.0 mM; $CaCl_2$: 2.2 mM; $MgCl_2$: 0.6 mM; NaH_2PO_4: 1.2 mM; and glucose: 12 mM. The solution was saturated with a mixture of 95% O_2 and 5% CO_2 that serves as a vehicle for volatile anesthetics, and pH was adjusted to 7.40 ± 0.02.

Ten Langendorff-perfused hearts were kept intact (nonfrozen hearts). In 20 other hearts, an endocardial cryotechnique was used to freeze the complete right ventricle, the interventricular septum, and the endocardial and intramural layers of the free wall of the left ventricle (frozen heart).[4,6] This cryotechnique was used to avoid epicardial breakthrough of longitudinal wave fronts from deeper layers and to allow complete and bidimensional mapping of electrical activation. Briefly, a cryoprobe was inserted through the pulmonary artery in the right ventricle, filled with liquid nitrogen (−192°C), and maintained in place until the right ventricle was completely frozen. The heart was then immersed in a tissue bath containing perfusion fluid at 30°C. The cryoprobe was placed in the left ventricular cavity through the left atrium, and the coronary circulation was temporary discontinued. The cryoprobe was filled with liquid nitrogen and maintained in place for 3 min. Thereafter, the coronary perfusion was restored, the probe was removed, and the heart was withdrawn from the tissue bath. Then, the temperature of the heart was kept constant at 37°C throughout the experiment. As a result of this procedure, only a thin epicardial layer (approximately 1 mm thick) of the free wall of the left ventricle survived, the rest of the myocardium was destroyed. It was previously shown that in this thin surviving layer, refractoriness and conduction velocity are not affected by the procedure and remain stable for hours, suggesting the adequacy of the circulatory condition in the epicardial layer.[12,13] At the end of the experiments, the hearts were dissected to verify the effectiveness of the cryoprocedure, and their results were excluded from the study if freezing was inadequate.

Protocol

Drug Administration. After a 60-min stabilization period, halothane (Fluothane; Zeneca Pharma, Cergy, France) or enflurane (Ethrane; Abbott, Rungis, France) were administered to the circuit by continuous energic bubbling, using calibrated vaporizers (Fluotec 3; Cyprane, Keighley, England, and Enflurane vapor 19.3; Drägerwerk AG, Lübeck, Germany). The bubbling chamber was covered, and the anesthetic vapor-tightness was made using a paraffin sheet. Anesthetic concentrations in the gas phase were monitored continuously using an infrared calibrated analyzer (Servo Gas monitor 120; Siemens-Elema). Each concentration (1, 3, and 5 vol%) was administered for 20 min. Electrophysiologic parameters were studied at baseline, after each concentration and after wash-out, in nonfrozen and frozen hearts.

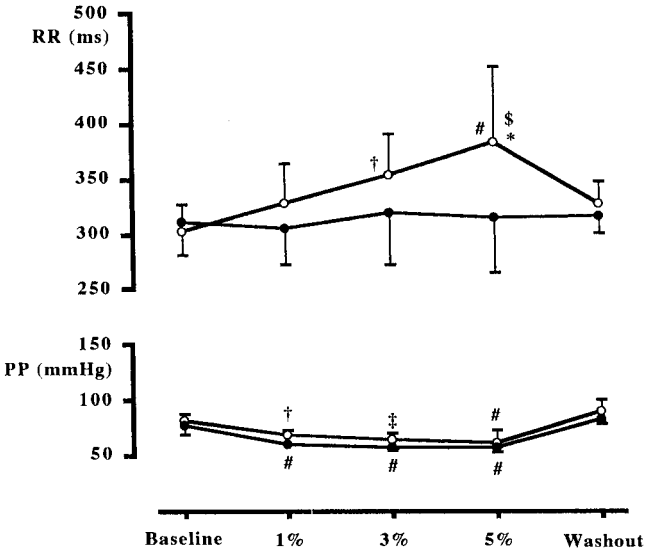

Fig. 1. Concentration–response curves of halothane (n = 5) and enflurane (n = 5) on spontaneous sinus cycle duration (RR, ms) and on perfusion pressure (PP, mmHg). Halothane (open circles) induced a concentration-dependent increase in RR interval, whereas enflurane (filled circles) did not. The perfusion pressure decreased with both agents, without concentration-dependence. #*P* < 0.001 *versus* baseline; ‡*P* < 0.01 *versus* baseline; †*P* < 0.05 *versus* baseline; $*P* < 0.05 *versus* 1%; **P* < 0.05 *versus* 3%.

Study of Arrhythmogenic Effects of Halothane and Enflurane in Nonfrozen Hearts. Halothane (n = 5) or enflurane (n = 5) were administered in nonfrozen hearts while in spontaneous sinus rhythm. Study variables were the spontaneous sinus cycle length (RR interval, expressed in ms), the perfusion pressure (PP, mmHg), and the occurrence of asystole or spontaneous arrhythmias. We expected to discontinue sustained monomorphic tachycardias by overdrive pacing and atrial or ventricular fibrillation by potassium chloride administration.

Study of Electrophysiologic and Arrhythmogenic Effects of Halothane and Enflurane in Frozen Hearts. Twenty frozen hearts were given halothane (n = 10) or enflurane (n = 10), administered to the perfusion fluid by bubbling, and the hearts were perfused with the solution. The study variables were ventricular conduction velocity, refractory period, and inducible arrhythmias. These arrhythmias were expected to be discontinued by the same methods used in nonfrozen hearts.

Data Acquisition System and Stimulation Protocol. High-resolution mapping of epicardial excitation was performed using a spoon-shaped electrode containing 256 unipolar electrodes at regular distances of 2.25 mm. The computerized mapping system allows simultaneous recording, storage and automatic analysis of all 256 electrograms, and on-line presentation of color-coded activation maps (Maptech system, Maastricht, The Netherlands).[14] Programmed electrical stimulation was performed using a programmable constant-current stimulator delivering square pulses of 2-ms duration at twice the diastolic threshold for regular stimulation and induction of premature beats (Maptech system). Bipolar stimulation could be performed using any pair of electrodes in the spoon electrode. The stimulation protocol used for the induction of arrhythmias consisted of (1) application of one, two, and three premature stimuli (S2, S3, and S4, respectively) delivered with decreasing coupling interval after 10 basic stimuli (S1–S1) at a 300-ms interval and (2) application of trains of 10 stimuli at a regular cycle length, which was progressively decreased at 10-ms steps until one-to-one capture of the ventricle failed (Fmax). This pacing protocol was applied in baseline conditions, after each dose of halothane or enflurane, and after wash-out. Spontaneous and inducible ventricular dysrhythmias were recorded and analyzed.

Electrophysiologic Measurements. The following parameters were measured: ventricular effective refractory period (VERP, expressed in ms), longitudinal ventricular conduction velocity (θL, cm/s), transverse ventricular conduction velocity (θT, cm/s), and the anisotropic ratio (θL/θT). During the experiment, these parameters were recorded using the same pacing site, which was located at the center of the thin surviving layer of the left ventricle. *VERP* was defined as the shortest S1–S2 interval still resulting in a propagated premature impulse after a train of 10 regular paced beats (S1–S1) at a cycle duration of 300 ms. A pause of 2,000 ms was introduced between successive trains. VERP was

Table 1. Concentration-dependent Effect of Halothane on Longitudinal (θL) and on Transverse (θT) Conduction Velocity, and on Anisotropic Ratio (θL/θT) (Frozen Hearts, n = 10)

	θL (cm/s)	θT (cm/s)	θL/θT
Baseline	69.8 ± 9.5	35.3 ± 5.8	2.00 ± 0.22
1%	68.5 ± 9.1	34.4 ± 7.0	2.05 ± 0.36
3%	64.1 ± 10.7*	32.3 ± 6.5†	2.02 ± 0.34
5%	55.8 ± 11.6*†‡	26.5 ± 5.2†§¶	2.11 ± 0.24
Washout	71.1 ± 11.4	34.5 ± 7.0	2.10 ± 0.34

θL, θT, and θL/θT were measured at PCL of 1,000 ms. Pacing site was located at the center of the left epicardium.

* $P < 0.01$ *versus* baseline.

† $P < 0.05$ *versus* baseline.

‡ $P < 0.01$ *versus* 1%.

§ $P < 0.05$ *versus* 1%.

¶ $P < 0.05$ *versus* 3%.

Table 2. Concentration-dependent effect of Halothane on Longitudinal (θL) and Transverse (θT) Conduction Velocity, VERP, Longitudinal (λL) and Transverse (λT) Wavelengths (Frozen Hearts, n = 10)

	θL (cm/s)	θT (cm/s)	VERP (ms)	λL (mm)	λT (mm)
Baseline	69.4 ± 9.2	35.4 ± 5.7	155.6 ± 12.5	109.3 ± 13.4	55.0 ± 9.8
1%	68.2 ± 11.1	34.0 ± 7.0	166.9 ± 16.9*	113.3 ± 18.4	56.7 ± 13.0
3%	63.5 ± 9.7	31.7 ± 6.4	165.5 ± 11.8	105.1 ± 17.6	52.3 ± 10.4
5%	54.7 ± 13.4	25.9 ± 5.7	157.4 ± 16.1	88.3 ± 22.7†‡§	40.7 ± 9.0†‡§
Washout	69.2 ± 10.4	34.0 ± 6.0	147.5 ± 12.3*	101.4 ± 12.6	49.8 ± 8.7

The pattern of significance of changes in θL and θT is similar to that reported in table 1, and is omitted for simplification. θL, θT, and VERP were measured at a PCL of 300 ms. Pacing site was located at the center of the left epicardium.

* $P < 0.05$ *versus* baseline.

† $P < 0.01$ *versus* 3%.

‡ $P < 0.01$ *versus* 1%.

§ $P < 0.001$ *versus* baseline.

determined by decreasing the coupling interval of the premature stimulus (S1–S2) in steps of 10 ms from 200 ms until the capture was lost, and then in steps of 1 ms for the last S1–S2 interval. To test the dispersion of repolarization over the left epicardium, VERP was measured for four sites in five hearts: main pacing site, apex, near the free wall of the left ventricle, and near the left anterior descending coronary artery.[6] As previously described by Clerc[15] and Spach *et al.*,[16] cardiac tissue has a different axial resistance along and perpendicular to the fiber axis of the myocardial fibers. This different axial resistance results in direction-dependent differences in conduction velocity (anisotropic conduction). Therefore, pacing at the center of the thin surviving layer of the left ventricle produced an ellipsoidal spread of propagation, allowing the identification of the myocardial fiber orientation, with fast conduction parallel to the fiber axis (longitudinal conduction, θL) and slow conduction perpendicular to the fiber axis (transverse conduction, θT). *Conduction velocity* was defined as the distance traveled by the wave front per unit of time. In each experiment, longitudinal and transverse conduction velocities and the anisotropic ratio were measured after 10 basic stimuli (S1–S1) at a 1,000-ms interval. In addition, to test the use–dependency of the drug, the longitudinal and transverse ventricular conduction velocities and the anisotropic ratio were measured after 10 basic stimuli at 900-, 800-, 700-, 600-, 500-, 400-, 300-, 250-, and 200-ms intervals. VERP was measured in four different sites, and the dispersion of refractoriness was quantified by the *index of dispersion* (DI), defined as the quotient of the standard deviation and the mean of VERP, and by the *maximal dispersion* (Dmax), defined as the difference between the maximum and the minimum values of VERP.[6] Finally, the *wavelength,* defined as the product of conduction velocity and VERP, was calculated for the longitudinal and transverse directions using respective conduction velocities measured at a pacing cycle length (PCL) of 300 ms.

Definition of Ventricular Dysrhythmias. We defined *ventricular dysrhythmias* as ventricular fibrillation (VF) and sustained (S) and nonsustained (NS) ventricular tachycardia (VT). A separation into monomorphic (M) and polymorphic (P) tachycardia was made.

Statistical Analysis

All study parameters were expressed as the mean ± SD. Data from nonfrozen hearts were analyzed by one-way analysis of variance for repeated measures. Data from frozen hearts were analyzed by two-way analysis of

Table 3. Dispersion of VERP in Frozen Hearts Treated with Halothane (n = 5)

	Site 1	Site 2	Site 3	Site 4	DI	D_{max}
Baseline	155.1 ± 11.1	151.6 ± 5.5	155.0 ± 6.1	154.2 ± 6.5	0.052 ± 0.040	18.00 ± 13.36
1%	168.8 ± 16.0	168.8 ± 10.7	169.0 ± 8.9	176.0 ± 8.1	0.049 ± 0.050	17.40 ± 21.21
3%	165.8 ± 13.6	162.4 ± 11.4	166.4 ± 12.9	173.2 ± 11.2	0.038 ± 0.013	12.40 ± 5.03
5%	157.4 ± 16.9	152.8 ± 14.1	154.6 ± 16.4	162.2 ± 16.5	0.048 ± 0.021	16.40 ± 5.68
Washout	152.5 ± 15.7	157.8 ± 12.7	152.6 ± 7.7	157.8 ± 5.3	0.049 ± 0.035	15.60 ± 8.76

VERP (in ms) was measured at a PCL of 300 ms. In each site, VERP values at 1% were significantly different from baseline (see table 2).

DI = dispersion index; D_{max} = maximal dispersion (in ms).

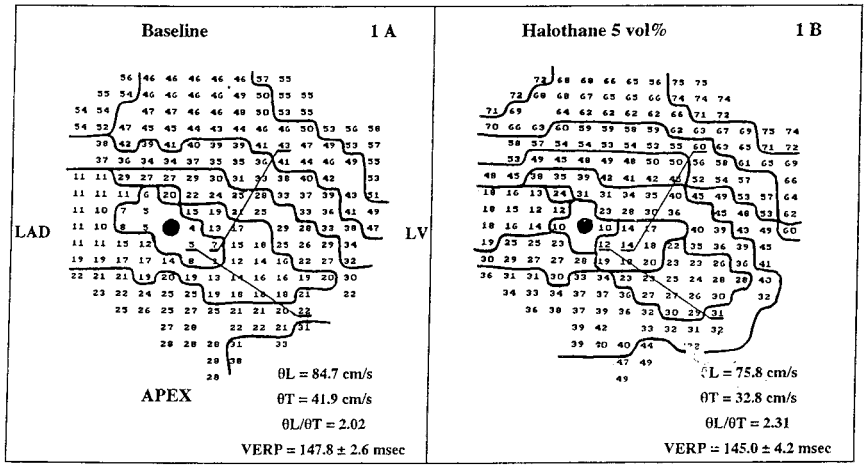

Fig. 2. Effects of 5% halothane in frozen hearts on longitudinal and transverse ventricular conduction velocities at a pacing cycle length (PCL) of 1,000 ms. The central closed circle represents the pacing site. Numbers indicate local activation times expressed in milliseconds. Isochrones are drawn at 10-ms intervals. The underlined activation times indicate the sites between which the longitudinal and transverse ventricular conduction velocities were measured in panels. Conduction velocities were slowed by 5 vol% halothane. The corresponding refractory period was unchanged. No functional conduction block occurred. θL = longitudinal ventricular conduction velocity; θT = transverse ventricular conduction velocity. LAD = left anterior descending coronary artery; LV = left ventricle.

variance for repeated measures, followed by a Neuman–Keuls test and Bonferroni correction, the two factors for analysis being volume percent and PCL. $P < 0.05$ was considered to be statistically significant.

Results

Effects of Halothane and Enflurane in Nonfrozen Hearts

The effects of halothane and enflurane on RR interval and on coronary perfusion pressure are reported in figure 1. Halothane induced a concentration-dependent bradycardia, whereas enflurane did not. Both anesthetics induced a decrease in the coronary perfusion pressure that was significant from 1 vol%, but that was not concentration-dependent. After wash-out, all parameters returned to baseline values. No spontaneous dysrhythmia occurred during and after halothane or enflurane administration.

Effects of Halothane and Enflurane in Frozen Hearts

Three hearts were excluded from the study because of excessive freezing (ineffective pacing), and 20 were included in the study. Conduction velocities and anisotropic ratio were measured during ventricular pacing at a PCL ranging from 1,000 to 200 ms. All hearts could be paced until a PCL of 200 ms, whatever the volatile anesthetic and its concentration. No ventricular dysrhythmia could be induced at baseline or after increasing concentrations of volatile anesthetics.

Halothane induced a concentration-dependent slowing of θL and θT that was significant from 3 vol% (table 1). Anisotropic ratio was unchanged. No significant use–dependency was observed, either on θL or on θT (data not shown). VERP was significantly prolonged at 1 vol%, and tended to decrease thereafter (table 2). There was no intersite variation, and the dispersion of VERP did not increase, as shown by minimal changes in index of dispersion and maximal dispersion (table 3). Changes in conduction velocity and VERP resulted in a slight and nonsignificant increase in wavelengths at 1 vol% halothane and a concentration-dependent decrease at higher concentrations, which was significant at 5 vol% (table 2). In figure 2, 5 vol% halothane-induced changes are shown in ventricular conduction velocities at a PCL of 1,000 ms.

Enflurane induced a concentration-dependent slowing of θL and θT that was statistically significant only at 5 vol% (table 4). The anisotropic ratio was unchanged. A significant use–dependency was observed on θL and on θT at 5 vol% and at a PCL of 250 and 200 ms (fig. 3). Indeed, θL decreased from 63.3 ± 5.8 cm/s at a PCL of 1,000 ms to 59.2 ± 6.3 cm/s at 200 ms ($P < 0.001$), and θT decreased from 33.5 ± 3.7 cm/s at a PCL of 1,000 ms to 30.8 ± 4.0 cm/s at 200 ms ($P < 0.001$). VERP was significantly prolonged at 1 vol% and also tended to decrease thereafter (table 5). Neither intersite variation in VERP nor changes in index of dispersion and maximal dispersion were observed (table 6). The wavelength decreased in a dose-dependent manner, and this was significant at 5 vol% (table 5).

Discussion

The current study shows, in isolated spontaneously beating rabbit hearts, that halothane decreased the RR

Table 4. Concentration-dependent Effect of Enflurane on Longitudinal (θL) and Transverse (θT) Conduction Velocity, and on Anisotropic Ratio (θL/θT) (Frozen Hearts, n = 10)

	θL (cm/s)	θT (cm/s)	θL/θT
Baseline	70.6 ± 7.2	36.6 ± 4.1	1.94 ± 0.14
1%	66.7 ± 4.4	35.1 ± 2.9	1.91 ± 0.17
3%	66.5 ± 5.4	34.8 ± 3.6	1.92 ± 0.19
5%	63.3 ± 5.8*†	33.5 ± 3.7*‡	1.91 ± 0.26
Washout	69.1 ± 7.7	34.9 ± 3.3	2.00 ± 0.25

θL, θT, and θL/θT were measured at PCL of 1,000 ms. Pacing site was located at the center of the left epicardium.

* $P < 0.05$ *versus* 1%.

† $P < 0.01$ *versus* baseline.

‡ $P < 0.05$ *versus* baseline.

interval, whereas enflurane did not. No spontaneous arrhythmia occurred. Both agents decreased the perfusion pressure. All these effects are well-known from experimental studies and in clinical practice.[1] In frozen hearts, both agents decreased θL and θT in a concentration-dependent manner, with no use–dependency, except at a PCL of 250 and 200 ms with 5 vol% enflurane. The anisotropic ratio did not change. VERP increased at 1 vol% and tended to decrease thereafter, with neither intersite variation nor changes in the dispersion parameters. Both agents induced a concentration-dependent decrease in wavelengths. However, neither conduction block nor dysrhythmias could be induced.

Effects on Conduction Velocities and on Cell-to-cell Coupling

Several studies investigated the effects of volatile anesthetics on myocardial conduction. It has been shown that these agents inhibit the fast inward sodium current (I_{Na}),[17,18] and that this results in a slowing of conduction velocity *in vivo*[19,20] in isolated hearts[21–24] and in cell preparations.[25–27] In adult guinea pig myocytes, Weigt *et al.*[17,18] demonstrated that the depressant effects of volatile anesthetics on inward sodium current is voltage dependent, and that, at a membrane holding potential of −80 mV (near physiologic membrane potential), 1.2 mM halothane induces a 43.6 ± 3.9% depression of Na^+ currents.[18] Therefore, significant decrease in the maximum upstroke velocity of the action potential (V_{max}) and depression of myocardial conduction by halothane could be expected. Data from the study of Ozaki *et al.*,[25] who used the microelectrode technique in guinea pig papillary muscle, confirm this hypothesis. These authors demonstrated that halothane and enflurane depress both the V_{max} and the conduction velocity. However, they showed that the slowing of conduction velocity is more pronounced than the decrease in V_{max}, suggesting a depression of the gap–junction conduction. Consequently, as changes in longitudinal conduction velocity mainly reflect V_{max} alterations,[28] the results of our study agree with that of Ozaki *et al.*[25] because only a modest slowing of this parameter occurred.

Previous studies showed that volatile anesthetics, especially halothane, alter the gap–junction conduction.[7,8] Our results are not in agreement with these findings. It could be argued that our model is not appropriate for the demonstration of such effect. Using this model, Brugada *et al.*[9] demonstrated that heptanol, which is well-known to depress gap–junction conduction, slows θT more than θL and therefore increases the anisotropic ratio (θL/θT),

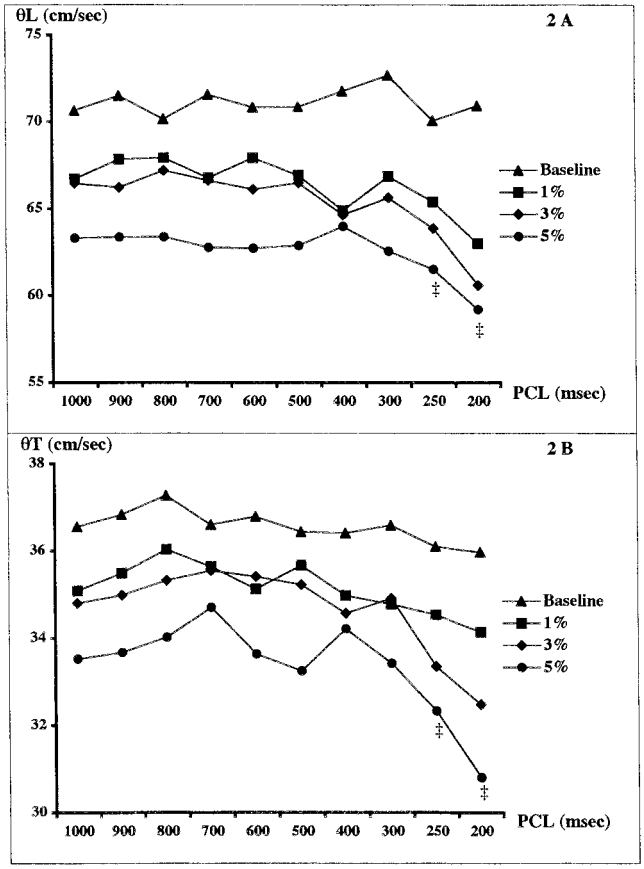

Fig. 3. Use-dependent effects on longitudinal (*2A*) and transverse (*2B*) conduction velocities of enflurane in frozen hearts. Data are expressed as the mean. Wash-out values and standard deviation bars are omitted for clarity. A use-dependency was noted at 5 vol% enflurane and at pacing cycle lengths (PCLs) of 250 and 200 ms. θL = longitudinal ventricular conduction velocity (expressed as cm/s); θT = transverse ventricular conduction velocity (expressed as cm/s); ‡$P < 0.001$ *versus* baseline.

Table 5. Concentration-dependent Effect of Enflurane on Longitudinal (θL) and Transverse (θT) Conduction Velocity, VERP, Longitudinal (λL) and Transverse (λT) Wavelengths (Frozen Hearts, n = 10)

	θL (cm/s)	θT (cm/s)	VERP (ms)	λL (mm)	λT (mm)
Baseline	72.7 ± 7.4	36.6 ± 4.2	152.4 ± 10.1	110.6 ± 11.7	55.7 ± 6.6
1%	66.9 ± 5.7	34.8 ± 3.2	162.6 ± 10.9†	108.5 ± 8.3	56.3 ± 4.0
3%	65.6 ± 6.6	34.8 ± 2.6	158.2 ± 8.5	103.8 ± 11.2	55.2 ± 4.3
5%	62.6 ± 6.3	33.4 ± 3.1	154.3 ± 12.6*	96.3 ± 9.9*†	51.5 ± 5.6*
Washout	67.2 ± 5.4	35.1 ± 4.4	156.3 ± 15.5	104.7 ± 9.4	54.6 ± 5.9

The pattern of significance of changes in θL and θT is similar to that reported in table 4, and is omitted for simplification. θL, θT, and VERP were measured at a PCL of 300 ms. Pacing site was located at the center of the left epicardium.

* $P < 0.05$ *versus* 1%.

† $P < 0.01$ *versus* baseline.

leading to transverse conduction blocks. Some hypotheses can be made to explain the discrepancy between our results and the results of others. The uncoupling effect might depend on the tissue species. Indeed, Freeman and Muir[26] demonstrated that halothane induces a marked slowing of the conduction through the Purkinje muscle junction without altering the conduction of Purkinje fibers. Tranum-Jensen *et al.*[29] showed that the Purkinje muscle junction is constituted of transitional cells that conduct the impulse slower than Purkinje fibers or ventricular myocytes. This might account for the conduction delay at the Purkinje muscle junction. Concerning the ventricular tissue, although the gap–junction conduction blockade by various agents can be observed at the microscopic size scale from studies using coupled cell pairs, this might be of minor importance in the whole-heart tissue because the ventricular muscle has an extensive cell-to-cell coupling.[30]

In our study, no significant use–dependency was observed in the absence of volatile anesthetics. This disagrees with previous studies in frozen hearts that showed that a use-dependent slowing of conduction occurs at a rapid PCL (less than 300 ms) and that this could result in conduction blocks and reentry.[12,31] This discrepancy could be a result of the animal species used. Nevertheless, in our experimental conditions, 5 vol% enflurane induced a use-dependent slowing of conduction at a 250- and 200-ms PCL, whereas halothane did not. The use–dependency with 5 vol% enflurane at a PCL of 250 and 200 ms did not lead to the occurrence of functional conduction block.

Effects on Refractoriness, Wavelengths and Implications for Arrhythmogenicity

Investigators previously showed that halothane and enflurane shorten the action potential duration at 50 or 90% repolarization[25,26] and lengthen the duration at 100% repolarization.[27] In our study, we found a biphasic effect of volatile anesthetics on VERP. Although no definitive explanation can be provided, this might be caused by the modulation by volatile anesthetics of different ionic currents involved in the myocardial recovery of excitability (voltage-, ion- and ligand-gated ionic currents) and from the concentration-related kinetic of their involvement.

In our study, halothane and enflurane did not increase the spatial dispersion of VERP. This is important because a drug that increases the dispersion of repolarization promotes functional conduction block and therefore reentrant arrhythmias.[6,10] The results of the current study suggest that halothane and enflurane cannot promote reentrant arrhythmias by this mechanism.

Table 6. Dispersion of VERP in Frozen Hearts Treated with Enflurane (n = 5)

	Site 1	Site 2	Site 3	Site 4	DI	D_{max}
Baseline	151.6 ± 11.9	153.4 ± 10.4	151.6 ± 14.6	153.6 ± 12.1	0.032 ± 0.018	12.20 ± 7.26
1%	165.2 ± 10.6	170.2 ± 17.2	173.8 ± 15.9	169.8 ± 10.6	0.042 ± 0.029	16.40 ± 11.72
3%	167.4 ± 14.2	168.8 ± 11.7	167.0 ± 11.2	173.8 ± 16.4	0.026 ± 0.013	9.40 ± 5.77
5%	164.6 ± 14.2	161.6 ± 14.1	163.6 ± 11.1	169.6 ± 16.5	0.028 ± 0.013	10.40 ± 5.32
Washout	163.6 ± 11.9	163.2 ± 13.8	151.7 ± 11.1	162.5 ± 13.3	0.056 ± 0.029*	20.20 ± 12.58*

VERP was measured at a PCL of 300 ms. In each site, VERP values at 1% enflurane were significantly different from baseline (see table 5). DI and D_{max} values at washout are different from those at baseline, 3% and 5%.

* $P < 0.05$.

Drugs that decrease wavelength tend to be arrhythmogenic.[2–4] Enflurane and especially halothane decreased the wavelengths at high concentrations, although we did not observe any arrhythmic event. No clear explanation can be given, but it appears that, because changes in conduction velocity and VERP were slight, the wavelengths did not decrease sufficiently to reach a critical value for reentrant arrhythmia. However, although the concept of critical wavelength is documented for atrial reentry,[32] data are lacking to specify the critical value of ventricles. Conversely, the lack of occurrence of conduction block and the lack of increased dispersion of repolarization also explain that no arrhythmia occurred.

Limitations of the Study

Because the volatile anesthetic solubility is temperature dependent and because we used a protein and fat-free solution, the actual concentration reaching the hearts may be less than that given, and probably ranged from 0.7 to 3.5 vol% for both agents, corresponding to calculated concentrations of approximately 0.26–1.32 mM.[33,34] In addition, one must keep in mind the difference in potency of halothane and enflurane when interpreting the results of the current study. Our data suggest that reentrant arrhythmias are unlikely to occur in normal hearts with both agents. However, care must be taken before extrapolating the current results to the clinical setting. First, the interaction of the hemodynamic status and of the autonomic nervous system with the intrinsic electrophysiologic properties of the ventricular myocardium are ignored in the model. Many data support the hypothesis that the use of volatile anesthetics in patients with high adrenergic tone could result in cardiac dysrhythmias. This is caused by the additive depressant effects of the adrenergic tone and of volatile anesthetics on inward sodium current.[35] In addition, it has been shown that volatile anesthetics enhance abnormal automaticity of normal Purkinje fibers exposed to epinephrine.[36] Second, our results of the electrophysiologic parameters are obtained from a thin epicardial layer. Because of slight differences in the electrophysiologic behaviors of cells constituting the ventricular wall,[37,38] other subtypes could be affected differently than epicardial ones and, theoretically, this could facilitate conduction blocks and reentrant arrhythmias. Finally, the safety of the use of volatile anesthetics in pathophysiologic cardiac conditions might be questioned. In situations such as hypoxia, hypercapnia, or electrolyte imbalance, serious disturbances of the cardiac electrophysiology may be expected, even in patients with healthy hearts. Similarly, the ischemia-associated changes in the cardiac electrophysiologic properties, especially conduction and refractoriness, and the autonomic imbalance that occurs in ischemic heart disease and myocardial infarction may facilitate, at least theoretically, the occurrence of arrhythmias with the use of volatile anesthetics. In fact, many data from cell preparations, isolated hearts, and animals show that halothane has genuine antiarrhythmic rather than proarrhythmic effects during myocardial ischemia or reperfusion.[1,36,39,40] This is caused, at least in part, by the fact that halothane blocks calcium channels, then opposes the mechanism for abnormal automaticity that promotes ischemia-associated arrhythmias.

Conclusion

The current study shows that halothane and enflurane slow longitudinal and transverse conduction velocity without inducing conduction blocks, even at high concentrations, or changing the anisotropic ratio. Both agents prolonged VERP at 1 vol% and reduced it at higher concentrations without increasing its spatial dispersion. The ventricular wavelength was decreased in a concentration-dependent manner. This suggests a proarrhythmic effect of these agents, but no dysrhythmias occurred in spontaneously beating hearts, and neither conduction block nor arrhythmias could be induced in frozen hearts.

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