Volatile Anesthetics Block Intercellular Communication Between Neonatal Rat Myocardial Cells
Janis M. Burt and David C. Spray

The effects of halothane and ethrane on gap junction-mediated intercellular communication and on membrane excitability were examined in cultured neonatal rat cardiac myocytes using whole-cell voltage-clamp and current-clamp techniques. Excitability was maintained at doses of both anesthetics that reversibly abolished current flow through junctional membranes. The degree of reduction of junctional conductance was a steep function of the dose of anesthetic; complete block occurred at lower aqueous concentrations of halothane than ethrane. The time course for loss of communication was rapid; 90% reduction of initial junctional conductance occurred in less than 15 seconds after exposure to 2 mM halothane or 4 mM ethrane. Recovery of junctional conductance and junctional permeability to intracellularly injected Lucifer yellow was rapid and complete on washout of the anesthetics. As junctional conductance was reduced by halothane or ethrane exposure, unitary conductance of the gap junctional channels remained constant at about 50 pS. Uncoupling by these anesthetics is thus attributable to a decrease in the number of conducting channels rather than to reduction of the channel’s unitary conductance. The data are discussed with regard to the possible role of this intercellular communication pathway in the arrhythmias and alterations of conduction velocity and contractility produced by volatile anesthetics. (Circulation Research 1989;65:829–837)

The gap junction has a well-defined role in cardiac tissue as a low-resistance pathway for propagation of the action potential. Conduction velocity is directly related to junctional conductance and both the upstroke velocity and amplitude of the action potential.1 The impact of decreased junctional conductance on the electrical properties (action potential duration, upstroke velocity, overshoot, or propagation delay) exhibited by individual cells of the cardiac syncytium is dependent on the intrinsic electrical properties (electrical properties exhibited by the cell when isolated from all neighbors) of that cell as well as those of its neighbors.2–4 Thus, to identify the mechanism underlying effects of an anesthetic on conduction velocity or on action potential characteristics exhibited by cells within a syncytium, it is necessary to evaluate the effects of the anesthetic on the conductance of the coupling pathway.

That volatile anesthetics influence gap junctional conductance was concluded by Hauswirth,5 Wojtczak,6 and Terrar and Victory.7 In Purkinje fibers, Hauswirth5 demonstrated that halothane reduced the space constant and resulted in a high degree of nonlinearity in spatial decay of potential. He proposed, as an explanation of these data, an increase in the resistance of the intercalated disk or even a “loosening” or loss of intercellular connections. In Purkinje fibers, Hauswirth5 demonstrated that halothane reduced the space constant and resulted in a high degree of nonlinearity in spatial decay of potential. He proposed, as an explanation of these data, an increase in the resistance of the intercalated disk or even a “loosening” or loss of intercellular connections. Wojtczak6 demonstrated a decrease in transgap action potential amplitude (trabeculae or papillary muscles, modified sucrose gap technique) during exposure to 3% halothane and attributed this decrease to loss of junctional conductance. In both of these studies, possible effects of the anesthetic on the nonjunctional membrane were not considered and thus do not resolve the extent to which junctional and nonjunctional conductances are affected. More recently, Terrar and Victory7 approached this question in a more rigorous manner. Using current injection and standard recording techniques, they demonstrated increased input and transfer resistances associated with uncoupling,
which would be consistent with decreased junctional conductance.

The influence of volatile anesthetics on the non-junctional membrane of cardiac cells has also been examined. Hauswirth demonstrated a significant reduction of action potential duration by halothane in isolated sheep Purkinje fibers and papillary muscle; this reduction was associated with a reduction of the refractory period. Smaller changes in resting potential, upstroke velocity, and overshoot were also noted. Lynch et al demonstrated that halothane depressed myocardial slow action potentials in guinea pig papillary muscles. Their findings suggest that activity of the slow inward current channel is depressed by halothane. This observation is consistent with the shortening of action potential duration observed by Hauswirth. Bosnjak and Kampine demonstrated significant alterations of the action potential of sinoatrial node cells, including decreased velocity of phase 4 and phase 0 depolarization and shortening of action potential duration. In the latter two studies, elevation of extracellular calcium only partially restored the action potentials toward control values. These studies indicate that the slow inward current channel was a target of halothane action but suggest that other membrane properties must also be affected to account for the alterations of refractory properties and especially of conduction velocity induced by halothane. In none of these studies were the possible effects of the anesthetic on junctional conductance considered. However, Terrar et al recently compared the effects of halothane and isoflurane on membrane currents of isolated guinea pig ventricular myocytes. They found significant reductions of slow inward currents and reduced action potential duration with both anesthetics, which is consistent with interpretations of previous studies.

The arrhythmogenic properties of volatile anesthetics, especially halothane, are well documented, but the underlying mechanisms are not well understood. Reductions in coupling strength and/or excitability would reduce conduction velocity and create discontinuities of electrical properties in the heart. These two alterations predispose cardiac tissue to reentrant type arrhythmias. In the present study the influence of halothane and ethane on junctional conductance and on excitability of cultured neonatal rat myocardial cells is measured. The data suggest that both anesthetics reduce junctional conductance and that halothane has a slightly greater potency than ethane. In addition, both anesthetics exert this effect at concentrations at which cellular excitability is maintained. The data are consistent with a possible role for decreased intercellular communication in the arrhythmogenic potential of volatile anesthetics and are discussed in terms of mechanisms of anesthesia as well as the cardiovascular side effects of the anesthetics.

**Materials and Methods**

Myocytes were isolated from neonatal rat hearts as described previously. Briefly, hearts from one or more litters of 12–36-hour-old neonatal rats were removed, rinsed in cold culture medium, minced into 1 mm³-pieces, and digested in six 10–15-minute periods in 0.175% pancreatin (GIBCO, Grand Island, New York) with gentle stirring at 37° C. The supernatants from digestion periods 4–6, which contained the released myocytes, were pelleted, resuspended in culture medium, preplated for 90 minutes to allow fibroblasts to adhere, and replated on glass coverslips at low density (60,000–76,000 cells/cm²). Cells were used for electrophysiological experiments 12–36 hours after plating; by this time, they had attached to the coverslip, flattened somewhat, and begun spontaneous contractile activity.

Coverslips with attached cells were mounted in a chamber and continuously suffused with either control or experimental solutions. Chamber volume was 1.5–2 ml and suffusion rate (except during anesthetic exposure; see below) was 5 ml/min. The presence or absence of cell-to-cell communication under control and experimental conditions was established qualitatively by noting whether intracellularly injected Lucifer yellow diffused into neighboring cells. Dye was dissolved in distilled water at a concentration of 5%. Electrodes were made from 1-mm thin-walled, fiber-filled glass, and dye was introduced into the electrode tips by capillary action. The electrodes (resistance, 15–30 MO) were back-filled with 2.7 M LiCl. Impalements were achieved by brief overcompensation of the negative capacitance compensation control on a bridge electrometer (model WPI 700, World Precision Instruments, New Haven, Connecticut). Dye diffused from the electrode into the cell passively although hyperpolarizing current (≤1 nA) was applied in some cases to facilitate injection.

For quantitative measurement of intercellular coupling, the dual whole-cell voltage-clamp technique was used on cell pairs identified as such by phase-contrast microscopy. Each of the cells was voltage-clamped to a common holding potential (usually 0 mV) with unpolished, patch-type microelectrodes connected to voltage-clamp circuits in the whole-cell configuration. Junctional current was measured in one cell during steps in the command potential (usually to -10 mV) of the other cell. Command potentials were applied to each cell sequentially to evaluate nonjunctional conductances. Junctional conductance was calculated as junctional current divided by the voltage step. For measurement of single gap junction channel events, the same recording configuration described above was used. However, a constant transjunctional potential of ±50 mV was used to visualize single channel events. Events of equal and opposite magnitude in the two current tracings represented gap junction channel events.
FIGURE 1. Phase contrast (left) and fluorescent micrographs of a pair of neonatal rat myocardial cells in culture for 28 hours and injected with Lucifer yellow while incubated in 2 mM halothane (center) and again after washout of the halothane (right). Note that dyes diffuse readily from the injected cell to its neighbor after washout of the halothane.

on a Gould Brush recorder (Gould Instruments, Cleveland, Ohio) with frequency response limited to <100 Hz and digitized and stored on videotape for further analysis and playback.

Excitability (capacity for action potentials) and propagation were measured during current clamp of cell pairs. Depolarizing current pulses of 10-msec duration were delivered to one cell of a pair at a frequency of 0.5–1 Hz. Action potentials elicited in the stimulated cell and extent of propagation to its neighbor were displayed on a 5000 series oscilloscope (Tektronix, Beaverton, Oregon) and recorded on tape for further analysis and playback. Whole-cell currents were also measured. Depolarizing steps (10-msec duration) of increasing amplitude (incremented by 10 mV) were applied from a holding potential of −90 mV, and peak inward current was measured.

Patch-type electrodes (5–10 MΩ) were prepared from fiber-filled 1.2-mm glass and filled with a solution well buffered with regard to protons and calcium (mmol/l): potassium glutamate 105, HEPES 10, EGTA 10, CaCl2 0.5, KCl 10, glucose 5, Na2ATP 5, adjusted to pH 7.2 with KOH. For the cells used in this study, the series resistance of the electrode (<10 MΩ) was always 1% or less of the input resistance (parallel sum of resistances of the seal and nonjunctional membrane) and was generally less than 10% of the junctional membrane resistance. Series resistance compensation had minimal impact on the recordings and was rarely used.

In the typical experiment, junctional properties were recorded before, during, and after an experimental intervention. During the control periods, the cells were usually suffused with a nominally calcium-free balanced salts solution (BSS) containing (mmol/l) NaCl 133, KCl 3.6, MgCl2 0.3, glucose 16, EGTA 0.5, and HEPES 3.0, pH 7.2 (adjusted with KOH), although use of calcium-containing BSS (1.0 mM CaCl2 without EGTA) did not alter the results. Excitability and propagation were also measured before, during, and after an experimental interven-

tion, and these measurements were obtained from cells bathed in calcium-containing BSS.

Anesthetics were introduced as follows. Stock solutions (calcium-free or calcium-containing BSS) saturated with anesthetic were diluted immediately before use. The saturated halothane and ethrane solutions were 17±1.6 mM and 14±0.6 mM, respectively; the values were determined by gas chromatography of hexane extracted samples (technique of Miller and Gandolfi21; n=4). Dilutions were made by drawing into a syringe (thereby minimizing the opportunity for volatilization) the appropriate volume of stock, briefly mixing the diluted solution by inversion of the syringe, and then injecting 50 ml diluted anesthetic through the suffusion lines to the dish at a rate of 25 ml/min. The diluted anesthetic was exposed to air only as it entered the experimental chamber where the flow rate provided complete exchange of the bath 25–33 times during the 1.5–2-minute exposure period. This procedure provided highly reproducible dose-response effects. The concentrations of anesthetic tested were 1–2 mM halothane, which corresponded to approximately 1–3%, and 2–4 mM ethrane, which corresponded to approximately 2–5%.7,11

Results

The uncoupling effect of 2 mM halothane and its reversibility are evident from dye-coupling studies (Figure 1). In this example, dye was injected into one cell of a pair after suffusing the cells with 50 ml of 2 mM halothane as described in the "Materials and Methods" section. No dye was detectable in the neighboring cell while halothane was present. After 5 minutes of suffusion with control solution (washing out the halothane), reinjection of dye into the same cell (necessary due to binding of previously injected dye to cellular components) demonstrated that coupling was restored. Consistent results were obtained in six cell pairs.

The time course and dose-response characteristics of uncoupling by halothane were determined
Halothane

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FIGURE 2. Tracings showing uncoupling of a pair of cardiac cells by increasing concentrations of halothane. Cells were clamped at 0 mV and stepped alternately to −10 mV (V<sub>1</sub> and V<sub>2</sub> represent voltage in cells 1 and 2, respectively). Upward deflections in the current tracings (I<sub>1</sub> and I<sub>2</sub>) represent current flow through junctional membrane; junctional current divided by the voltage step equals junctional conductance. (Downward deflections in the current tracings represent the sum of junctional and nonjunctional currents.) Note the partial and complete loss of junctional current during exposure to 1.5 and 2 mM halothane, respectively. Full recovery of coupling occurred after each dose (although not shown for 2 mM halothane). Calibrations are for each panel.

Using the dual whole-cell voltage-clamp technique, Figure 2 illustrates the response of a cell pair to increasing concentrations of halothane. Each anesthetic exposure involved suffusion of 50 ml into the dish over a 1.5-2-minute period. One millimolar halothane appeared to have only a slight effect, 1.5 mM reduced coupling by 90% over the 2-minute period, and 2 mM halothane reduced coupling to unmeasurable levels. The time courses for uncoupling by halothane at these doses are illustrated for a number of cell pairs in Figure 4A. With respect to the effect of halothane on junctional conductance, the fact that steady state was not seen during exposure to 1 mM or 1.5 mM halothane suggests that the 1.5-2-minute suffusion period was insufficient for the cells to fully equilibrate with the anesthetic. In contrast, the complete uncoupling by 2 mM halothane before suffusion was terminated indicates that this concentration exceeds that necessary for complete uncoupling. These data indicate a steep dose-response curve for the anesthetic on junctional conductance. In each case coupling recovered toward normal levels on washout of the anesthetic.

Figure 3 illustrates the response of a cell pair to increasing doses of ethrane. For the 2-mM and 3-mM exposures, 50 ml diluted anesthetic was suffused through the dish over the indicated time period, analogous to the halothane experiments illustrated in Figure 2. For the 4 mM ethrane experiment (Figure 3, bottom left), the exposure to anesthetic was stopped shortly after complete uncoupling had occurred; an exposure to halothane of comparable duration is also shown (Figure 3, bottom right). Two millimolar ethrane had little or no effect on coupling, 3 mM ethrane produced 80% uncoupling during the 2-minute exposure, and 4 mM ethrane completely and rapidly uncoupled the cardiac cells. In each case there was virtually complete recovery of junctional conductance from the anesthetic. Interestingly, recovery from the short exposure to 2 mM halothane occurred significantly faster than did recovery from longer exposures (compare bottom panels of Figures 2 and 3). These recovery rates further support the conclusion that this concentration exceeds that necessary for complete closure of all gap junction channels. The time courses for uncoupling for these doses of ethrane are illustrated for a number of cell pairs in Figure 4B. These data indicate that cardiac gap junctions are indeed influenced by ethrane. However, higher concentrations of ethrane than halothane are required for uncoupling.

The reduction in intercellular coupling could occur by decreasing the unitary conductance of the gap junction channel, by reducing its open time properties, or by reducing the number of channels present in the junction.\(^2\) We have previously shown that the unitary conductance of the cardiac gap junction channel is 53±2 pS and is not affected when junctional conductance is reduced by acidification or exposure to heptanol.\(^9\) Single channel events
Figure 3. Tracings showing uncoupling of a pair of cardiac cells by increasing concentrations of ethrane. Cells were clamped at 0 mV and stepped alternately to −10 mV (V₁ and V₂ represent voltage in cells 1 and 2, respectively). Upward deflections in the current tracings (I₁ and I₂ for cells 1 and 2, respectively) represent current flow through junctional membrane; junctional current divided by the voltage step equals junctional conductance. (Downward deflections in the current tracings represent the sum of junctional and nonjunctional currents). In the 4 mM ethrane and 2 mM halothane experiments, exposure to anesthetic was stopped shortly after complete uncoupling. Note the different rates of recovery of coupling after short versus long exposures (see Figure 2). Calibrations are for each panel.

observed when junctional conductance was lowered by exposure to 2 mM halothane are illustrated in Figure 5A, and the histogram of the amplitudes of 204 events (five cell pairs) is illustrated in Figure 5B. The average amplitude for each cell pair was 57 ± 1.8 pS (n = 55), 50 ± 1.1 pS (n = 50), 40 ± 1.3 pS (n = 28), 53 ± 1.2 pS (n = 37), and 45 ± 1.2 pS (n = 34). The average for these cell pairs was 49 ± 3 pS (n = 5), and for all of the events illustrated in Figure 5B, independent of cell-pair origin, the average was 53 ± 1 pS. These values for unitary conductance are not different from previously published values obtained for the cardiac gap junction under control conditions or after exposure to other uncoupling agents.19

To determine the relative sensitivity of the voltage-gated currents, which underly excitability, compared with the gap junction channels to these anesthetics, potentials and currents were measured under current-clamp conditions in cell pairs before, during, and after exposure to halothane or ethrane (Figure 6A–6C). Figure 6A demonstrates impulse propagation between cells under control conditions. Exposure to 2 mM halothane caused uncoupling, but cells remained excitable (Figure 6B and 6C). Successful propagation was restored as coupling recovered (Figure 6D) on washout of the anesthetic. Under whole-cell voltage-clamp conditions, currents obtained from single cardiac cells before and during exposure to 2 mM halothane (50 μl anesthetic superfused over the cells, analogous to the experiments in Figure 2) or 4 mM ethrane revealed no change in peak inward current amplitude. (During halothane exposure, peak inward current was 120 ± 19% [n = 3] of control levels; during ethrane exposure, peak inward current was 95 ± 3% [n = 3] of control levels.) At higher concentrations of halothane (4 mM), the amplitude of the action potential measured during current clamp was reduced. This effect was particularly pronounced in cells whose resting potential was in the −60 to −70 mV range (Figures 7A–7C). Similarly, in voltage-clamp experiments, peak inward current was reduced (63 ± 5% of control) by higher anesthetic concentrations. These data indicate that excitability is maintained at concentrations of anesthetic that completely block intercellular communication via gap junctions in these cells.

Discussion

The studies presented here demonstrate that the conductance of cardiac gap junctions is reduced by the volatile anesthetics, halothane and ethrane. This uncoupling effect is observed at anesthetic concentrations that do not dramatically alter cardiac cell excitability; this finding is consistent with previously measured responsiveness of Na⁺ and K⁺ channels to similar doses of these anesthetics.23 These observations raise the possibility that alterations of the action potential produced by these anesthetics in syncytial preparations of heart (at similar, clinically relevant doses) may reflect alter-
ations of cell-to-cell coupling rather than or in addition to alterations of the intrinsic electrical properties of the cells.

In areas of the heart that are homogeneous with respect to intrinsic membrane properties (e.g., in the ventricle or atrium), a reduction in junctional conductance is expected to reduce contractility due to decreased synchrony of force development across the syncytium. Synchronization of force development in a syncytial tissue is dependent on minimal delay between activation of the first and last cells in the syncytium, which is a function of the conduction velocity. Conduction velocity varies inversely with the square root of the longitudinal internal resistance, which is the sum of cytoplasmic and junctional resistances. Thus, as the resistance to

![Figure 4](image-url)  

**Figure 4.** Graphs showing time course for uncoupling by halothane (panel A) and ethrane (panel B). Junctional conductance ($G_j$) was normalized such that the conductance immediately before exposure to anesthetic was considered 100%, and subsequent changes in conductance were calculated as a percentage of the initial conductance. Each time point represents the mean±SEM of the response of cells upon first exposure to the anesthetic at the relevant concentration. For 2 mM halothane, n=8; for 1.5 mM halothane, n=4; for 1 mM halothane, n=3; for each ethrane curve, n=3.

![Figure 5](image-url)  

**Figure 5.** Tracings of single channel events during the early recovery period after uncoupling by 2 mM halothane (panel A) and a histogram of the amplitudes of these events (panel B). Currents from cells 1 and 2 ($I_1$ and $I_2$) are shown during voltage clamp of cell 1 at -45 mV and cell 2 at 0 mV. Single gap junction channel events are recognized by their equal amplitude but opposite polarity in the two tracings. The current tracing for cell 1 is “noisier” due to nonjunctional channel activity that is inactivated at 0 mV in cell 2. At the start of this record, junctional conductance was 30 pS; at the end, junctional conductance was 0 pS, and peak conductance was 200 pS (equivalent to four channels open simultaneously). Opening events are upward in $I_2$ and downward in $I_1$. Junctional conductance before and after halothane exposure was 24 nS (480 channels open simultaneously). Events recorded in the histogram were derived from records similar to that shown in panel A and were measured by hand. Bin size is 10 pS.
propagation from cell to cell increases, conduction velocity decreases, synchronization of force development of the individual cells of the syncytium is delayed, and contractility is reduced. To the extent that calcium influx, calcium release within the cells, and calcium binding by the myofilaments are compromised by similar concentrations of these anesthetics,11,25 the effects on contractility of slowed conduction velocity and reduced availability of calcium would be additive. Thus, by simply increasing the resistance of the intercellular communication pathway or by combining this effect with other effects of anesthetics on the processes involved in excitation-contraction coupling, the net result of the anesthetics is reduced contractility.

In parts of the heart that are nonhomogenous with respect to intrinsic membrane properties (e.g., those occurring naturally at the sinus node–atrium or Purkinje-ventricular junctions or those induced by abnormal conditions such as ischemic injury), the effects of increased coupling resistance are not always intuitive (see Reference 3). As cells uncouple from one another, the action potentials of the different cells approach those exhibited by the cells in isolation (i.e., action potential dictated by the intrinsic membrane properties of the individual cells). Changes in cycle length (phase 4 depolarization) and maximum rate of rise of the action potentials are expected; for some cells there may be increases in these parameters; for others there may be decreases. As inhomogeneity develops, an increase in the incidence of arrhythmias is expected.12,13,26 This occurs largely through delays in propagation (slowed conduction velocity), which predispose the
tissue to reentrant type arrhythmias (see Reference 26 for discussion of the basis of reentrant arrhythmias) and increase the occurrence of and susceptibility to the activity of ectopic foci.

The mechanism(s) underlying closure of the gap junction channel by these anesthetics is uncertain. Possibilities include direct effects on the channel, through binding to the channel or alteration of the lipid environment around the channel, or indirect effects on the channel, for example, through reduction of intracellular pH or pCa. Closure of the channel by volatile anesthetics does not likely involve reduction of either intracellular pCa or pH. This conclusion stems from the fact that uncoupling occurred in the presence of strong intracellular buffering for both of these ions and when extracellular calcium was either at normal levels (1 mM) or reduced levels (0.5 mM EGTA without added calcium). With regard to a direct effect on the channel, the data do not allow distinction between direct binding of these anesthetics to the channel proteins compared with alterations of the lipid environment around the channel. The widely varying structures of the lipid soluble substances to which the gap junction channel is sensitive, such as octanol and heptanol,17,19, 27 halothane and ethane (present results), doxyl stearic acid,28 might suggest a mechanism involving nonspecific lipid effects. However, direct interaction of these molecules with gap junction channels seems likely in view of the following observations. First, only alkanols of a limited chain length (heptanol and octanol) influence the gap junction channel.27 Second, for the fatty acid derivative, doxyl stearic acid, both the negative charge and membrane-perturbing doxyl group are necessary for block of the gap junction channel.28 And third, when the potency (product of lipophilicity and effective aqueous concentration) of these agents is compared, it is apparent that octanol is a more potent uncoupler than either halothane or ethane. (The partition coefficients for halothane [phosphatidylcholine bilayer/water], ethane [oils/water], and octanol [phosphatidylcholine/water] are 123, 124, and 387, respectively,23,29 and their effective aqueous concentrations [for complete block] are 2 mM, 4 mM, and 300 µM, respectively [personal observation].) These observations, together with those of others,30–32 support a mechanism involving direct interaction of the anesthetics (or other lipid soluble substances) with "susceptible" membrane proteins.

Regardless of the direct or indirect nature of the anesthetic-induced response, closure of the gap junction channel does not involve a change in the unitary conductance of the channel. The single channel records are suggestive of a reduction in mean channel open time in the presence of the anesthetics but do not permit distinction between reduced probability of opening or enhanced probability of closing or a combination thereof. This result is similar to that observed for volatile anesthetic interaction with the acetylcholine receptor channel and a cholinergic synapse.33,34

In summary, our data demonstrate sensitivity of cardiac gap junctional conductance to concentrations of volatile anesthetics that do not block cardiac cell excitability and are relevant to clinical use of these anesthetics.7,11 The data thus support the hypothesis that reduction of intercellular coupling during exposure to these anesthetics contributes to the depression of myocardial contractility and the occurrence of arrhythmias.

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