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Myocardial Depressant Effects of Desflurane

Mechanical and Electrophysiologic Actions In Vitro

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Background: **The authors determined whether desflurane altered myocardial excitation–contraction coupling and electrophysiologic behavior in the same manner as isoflurane and sevoflurane.**

Methods: **The effects of desflurane on isometric force in guinea pig ventricular papillary muscles were studied in modified standard and in 26 mM K^+ Tyrode solution with 0.1 μM isoproterenol. Desflurane effects on sarcoplasmic reticulum Ca^{2+} release were also determined by examining its actions on rat papillary muscles, guinea pig papillary muscles in low-Na^+ Tyrode solution, and rapid cooling contractures. Normal and slow action potentials were recorded using a conventional microelectrode technique. Ca^{2+} and K^+ currents of guinea pig ventricular myocytes were examined.**

Results: **Desflurane (5.3% and 11.6%) decreased peak force to approximately 70% and 40% of the baseline, respectively, similar to the effects of equianesthetic isoflurane concentrations. With isoproterenol in 26 mM K^+ Tyrode solution, desflurane markedly depressed late peaking force and modestly depressed early peak force. The rested state contractions of rat myocardium or guinea pig myocardium in low-Na^+ Tyrode solution were modestly depressed, whereas rapid cooling contractures were virtually abolished after desflurane administration. Desflurane significantly prolonged the action potential duration. Desflurane reduced L-type Ca^{2+} current and the delayed outward K^+ current but did not alter the inward rectifier K^+ current.**

Conclusions: **Myocardial depression by desflurane is due to decreased Ca^{2+} influx, whereas depolarization-activated sarcoplasmic reticulum Ca^{2+} release is modestly depressed, similar to the actions of isoflurane and sevoflurane. Desflurane depressed the delayed outward K^+ current associated with significant lengthening of cardiac action potentials.**

DESFLURANE, a structural analog of isoflurane, is a volatile anesthetic that possesses low blood gas solubility,[1] providing rapid induction and emergence from anesthesia. During maintenance of desflurane anesthesia, a mild decrease in systemic arterial pressure has been reported clinically.[2] Dose-related depression of left ventricular function or cardiac output by desflurane has been demonstrated in *in vivo* animal studies[3–6] as well as in humans.[7] Direct myocardial depression by desflurane has been demonstrated *in vivo* using dogs subjected to pharmacologic blockade of their autonomic nervous system,[6] and *in vitro* using guinea pig (GP) hearts[8] and human atria.[9] Despite these findings, recent studies using isolated myocardial preparations in rats[10] and hamsters[11] indicated no significant effect on myocardial contractility. Although a modest effect of desflurane on sarcoplasmic reticulum (SR) function and indirect evidence for inhibition of Ca^{2+} entry have been proposed in isolated myocardial preparations,[10,11] the mechanisms underlying direct myocardial depression has not been well defined. Therefore, the current study was undertaken to determine the direct inotropic effects of desflurane and to elucidate the mechanisms by which desflurane causes contractile depression using a variety of experimental myocardial models, inotropic interventions, and electrophysiologic methods that had been previously used in the study of other volatile anesthetics.[12–15]

Materials and Methods

Effects on Contractility

Experiments with Modified Standard Tyrode Solution. According to a procedure approved by the Yonsei University College of Medicine Animal Research Committee (Seoul, Korea), the heart was removed from 400- to 450-g female GPs or rats (Sprague-Dawley) after halothane anesthesia (2.5–4 vol%). Next, the right ventricular papillary muscles were excised, mounted horizontally in a tissue bath, and superfused (8 ml/min) at 37°C with modified standard Tyrode solution (118 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3^-$, 11 mM glucose, 0.10 mM EDTA). EDTA was used to chelate any trace contaminant heavy metals. The solution was circulated through a bath from an unsealed reservoirs through which a mixture of 95% O_2 and 5% CO_2 was bubbled (flow rate: 0.5 l/min) to maintain a pH of 7.4 ± 0.05. The tendinous end of the papillary muscle was attached to a Grass FT03 force transducer (Grass Instruments, Quincy, MA) while the other end of the muscle was pinned to the bottom of the tissue bath. The length of the muscle was adjusted to the lowest resting force at which maximum twitch force was obtained. The muscles were field-stimulated using a Grass S44 stimulator (Grass Instruments) at 120% of stimu-

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lus threshold at 0.5 Hz for 60 min for stabilization. After a 15-min rest, a rested state (RS) contraction was elicited, followed by stimulation rates of 0.1, 0.5, 1, 2, and 3 Hz, sequentially. At each stimulation rate, the duration of stimulation was preset and kept constant during the experiment. After baseline measurements, the muscles were successively exposed to 6% and 12% desflurane (vaporizer setting) or 1.15% and 2.3% isoflurane (vaporizer setting), each for 15 min, at which the response were recorded. In pilot experiments, a 15-min application of desflurane was sufficient to produce a stable and consistent effect. Recovery responses were measured after a 20-min washout period. Effects on contractile function were estimated from the peak force (PF) and maximum rate of force development (dF/dt-max).

Effects of Desflurane on Catecholamine-mediated Responses. To examine the effects of desflurane on catecholamine release from the ventricular myocardium,[10] both receptor blockade and catecholamine depletion were used. In an initial control study, a positive inotropic response to tyramine (30 μM) was used to verify that the GP ventricular myocardium has catecholamine-containing sympathetic nerve endings.

In the first experimental series, muscles were exposed to phentolamine (1 μM) and propranolol (1 μM) to prevent catecholamine activation of α and β adrenoceptors on the cardiac membrane. After a 15-min pretreatment and measurement of baseline contractile forces, contractions were recorded after a 15-min application of desflurane. Recovery was observed after a 20-min washout period (phentolamine and propranolol were maintained throughout). In a separate experimental group, a lack of response to a 15-min application of tyramine (30 μM) was used to verify that the blockade of adrenoceptors by phentolamine and propranolol was adequate.

In the second experimental series, the ventricular myocardium was depleted of catecholamines by an intraperitoneal injection of reserpine (4 mg/kg) into the GPs 24 h before the experiment.[16] The depletion of catecholamine was verified by the absence of a positive inotropic response to an occasional threefold increase of stimulus voltage during the 60-min stabilization period, because high stimulus intensity can activate catecholamine release from sympathetic nerve endings. Contractile measurements were taken during control conditions, after a 15-min application of 6% desflurane, and after a 20-min washout. In a separate experimental group, the depletion of catecholamine by reserpine was also verified by a lack of contractile enhancement after treatment with tyramine.

Evaluation of Sarcoplasmic Reticulum Function In Situ

Rat Papillary Muscle. Rat papillary muscles were used to evaluate the effects of desflurane on contractions caused almost exclusively by Ca^{2+} release from the SR. After baseline measurements at RS, the muscles were exposed to 12% desflurane for 15 min. Recovery responses were measured after a 20-min washout.

Experiments with Low-Na^+ (25 mM) Tyrode Solution. Experiments using GP papillary muscles in low-Na^+ (25 mM) Tyrode solution (25 mM $NaHCO^-_3$, 5 mM KCl, 2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 11 mM glucose, 0.1 mM EDTA, 234 mM sucrose) were performed to confirm the effect of desflurane in rat force studies and to rule out the species-dependent differences in SR Ca^{2+} release. After obtaining baseline measurements at RS after a 15-min rest, muscles were exposed to 12% desflurane for 15 min. Recovery responses were measured after a 20-min washout.

Rapid Cooling Contracture. When isolated strips of myocardium are rapidly cooled, a contracture develops as a result of sudden release of Ca^{2+} from the SR,[17] used as an index of the SR Ca^{2+} content. Using GP papillary muscles, stimulation was gradually increased from 0.1 to 2 Hz until a stable contraction was obtained. The duration of stimulation at each stimulation rate was preset and kept constant during the experiment. Immediately after the abrupt cessation of the stimulus, a rapid cooling contracture (RCC) was triggered by rapidly changing the perfusion of modified standard Tyrode solution (flow rate: approximately 50 ml/min) from 37°C to 0°C, which decreased the temperature to less than 5°C within 2–4 s. Cooling was maintained for 60 s, after which perfusion with 37°C modified standard Tyrode solution was resumed. After determination of the control response, the identical protocol was repeated after a 15-min exposure to 6% desflurane, a 15-min exposure to 12% desflurane, and lastly after a 20-min washout. Isometric force and bath temperature were continuously recorded during the experiment.

Experiments with Isoproterenol Stimulation (in 26 mM K^+ Tyrode Solution). β-Adrenergic stimulation with 0.1 μM isoproterenol enhances contractility by increasing Ca^{2+} entry *via* L-type Ca^{2+} ($I_{Ca,L}$) channels[18,19] as well as an increasing Ca^{2+} uptake into and release from the SR.[20] When applied in 26 mM K^+ Tyrode solution (97 mM NaCl, 26 mM KCl, 2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM $NaHCO^-_3$, 11 mM glucose, 0.1 mM EDTA), there is partial depolarization of the myocardium to −40 to −45 mV, which inactivates fast Na^+ channels, while permitting conduction of slow action potentials (APs) (mediated by $I_{Ca,L}$). After recording the biphasic contractions[12,13,15,21] under control conditions at RS up to 3-Hz stimulation rate, contractions at the same stimulation rates were recorded after application of 6% and 12% desflurane (applied sequentially for 15 min each). Recovery responses were measured after a 20-min washout.

After each force experiment, muscle cross-sectional area was estimated from muscle length, weight, and density (1.04 g/ml), assuming a cylindrical form. Mean cross-sectional areas were 0.82 ± 0.37 mm^2 (n = 65,

from 0.24 to 1.99 mm^2) and 0.81 ± 0.26 mm^2 (n = 5, from 0.54 to 1.15 mm^2) in GPs and rats, respectively.

Electrophysiologic Studies

Papillary Muscle APs. Papillary muscle membrane potential was monitored with conventional 3 M KCl–filled glass microelectrodes (10–20 MΩ) attached to a VF-1 preamplifier (World Precision Instruments, Sarasota, FL). Membrane potential and its maximum rate of rise during the AP (dV/dt-max) were monitored on a digital storage oscilloscope. Because the vigorous contractions at higher stimulation rates (2 and 3 Hz) often caused dislodgement of impaled microelectrodes, only results from an impalement maintained throughout the whole sequence at 0.25-Hz stimulation rate were tabulated. Stimulation intensity was maintained at approximately 120% of the lowest intensity necessary to elicit a response and then adjusted to maintain approximately the same latency (stimulus–action potential interval, usually 5–10 ms). AP amplitude, dV/dt-max, and AP duration at 50% and 90% of repolarization (APD_{50} and APD_{90}, respectively) were measured at 0.25-Hz stimulation rate in modified standard Tyrode solution and in 26 mM K^+ Tyrode solution with 0.1 μM isoproterenol.

Isolated Myocyte Studies.

Isolation of Ventricular Myocytes. Guinea pigs (approximately 300 g) were anesthetized with halothane at 2.5–4 vol%. The heart was quickly excised and retrogradely perfused using a Langendorff perfusion system. The heart was perfused for 5 min at 37°C at a rate of 7 ml/min with modified Tyrode solution (143 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 0.5 mM $MgCl_2$, 5 mM HEPES, 0.18 mM glucose, pH 7.4). The perfusate was then switched for 5 min to a nominally Ca^{2+}-free Tyrode solution followed by perfusion with the same solution to which collagenase (0.4 mg/ml, Worthington type II; Worthington Biochemical Corporation, Lakewood, NJ) and protease XIV (0.04 mg/ml; Sigma-Aldrich Co., St. Louis, MO) had been added. After a 10- to 12-min enzymatic treatment, Kraftbrühe solution (10 mM taurine, 10 mM oxalic acid, 70 mM glutamic acid, 35 mM KCl, 10 mM H_2PO_4, 11 mM glucose, 0.5 mM EGTA, 10 mM HEPES, pH 7.4) was perfused for 5 min. The ventricles were then cut off and minced with scissors and agitated in a small beaker with Kraftbrühe solution, and the resulting slurry was filtered through a 200-μm nylon mesh. The isolated ventricular cells were stored in Kraftbrühe solution for 1 h at room temperature (21°–22°C), kept at 4°C, and used within 8 h. Only the rod-shaped cells with apparent striations that remained quiescent in the solution containing 2 mM $CaCl_2$ were used for the experiments. All patch clamp experiments were conducted at room temperature.

Electrophysiologic Techniques. Isolated myocytes were allowed to settle to the bottom of a recording chamber mounted on an inverted microscope where the bathing solutions could be exchanged. The chamber was continuously perfused at a rate of 2 ml/min. Standard whole cell voltage clamp methods were used.[22] After the initiation of the whole cell recording configuration, an interval of 4–6 min was allowed to establish a stable baseline. Voltage clamp measurements were performed using an Axopatch 200B patch clamp amplifier (Axon Instruments, Foster City, CA). Patch electrodes were prepared from a borosilicate glass model KIMAX-51 (American Scientific, Charlotte, NC), which have a typically 2–3 MΩ resistance when filled with an internal solution. After fabrication with a two-stage micropipette puller, the pipette tips were heat-polished with a microforge. Data acquisition was performed using a pCLAMP system version 6.0 (Axon Instruments) coupled with a Pentium III personal computer.

Voltage Clamp Protocols. Simultaneous recordings of delayed outward K^+ current (I_K) and inward rectifier K^+ current (I_{KI}) were obtained using a linear voltage ramp protocol in which the cells were held at −40 mV before sweeping the membrane potentials from −130 to +50 mV at a rate of 30 mV/s. For the detailed evaluation of desflurane effect on I_K, the I_K was measured by step depolarizations from −30 to +80mV with a holding potential of −40 mV in 20-mV increments, 5-s intervals, and 4-s pulse duration. The voltage-dependent $I_{Ca,L}$ was evoked by step depolarization lasting 200 ms from a holding potential of −40 to +10 mV in one step at a frequency of 0.1 Hz.

Solutions. An external bathing solution (140 mM NaCl, 5.4 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 5 mM HEPES, 10 mM glucose, adjusted to pH 7.4 with 1N NaOH) was used before establishing the whole cell recording. For K^+ current measurements, a patch pipette solution (20 mM KCl, 110 mM K-aspartate, 10 mM EGTA, 10 mM HEPES, 1 mM $MgCl_2$, 5 mM K_2ATP, 1 mM $CaCl_2$, 10 mM NaCl, adjusted to pH 7.2 with KOH) was used before establishing the whole cell recording configuration. After establishing the whole cell voltage clamp, 0.2 mM $CdCl_2$ was added to the external bathing solution to eliminate any confounding Ca^{2+} current. Inward Ca^{2+} currents were measured using a patch pipette solution (30 mM CsCl, 100 mM aspartic acid, 100 mM CsOH, 10 mM BAPTA, 10 mM HEPES, 10 mM phosphocreatinine, 1 mM Na_2GTP, 5 mM Na_2ATP, 10 mM glucose, 2 mM $MgCl_2$, adjusted to pH 7.25 with 1 M CsOH). Upon obtaining the whole cell recording, the external bathing solution was exchanged to a solution (140 mM NaCl, 5.4 mM CsCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, adjusted to pH 7.4 with 1 M CsOH) to measure $I_{Ca,L}$.

After the baseline measurement, the myocytes were exposed to 6% or 12% desflurane for 2 min. Recovery responses were measured after a 2-min washout. In pilot experiments, a 2-min application of desflurane was sufficient to produce a stable and consistent effect.

Drugs and Chemicals

In contraction and AP experiments at 37°C, desflurane or isoflurane was equilibrated with solution in one reservoir by passing the 95% O_2–5% CO_2 gas mixture (flow rate: 0.5 l/min) through a desflurane (Devapor Type M32600; Dräger AG, Lübeck, Germany) or isoflurane (Isotec 3; Ohmeda, West Yorkshire, United Kingdom) vaporizer for 15 min. The end-tidal concentrations of desflurane or isoflurane were monitored with a gas analyzer (Capnomac; Datex, Helsinki, Finland) that had been calibrated before use. Isoflurane was used to compare contractile parameters with approximately equianesthetic concentrations of desflurane.

As determined by gas chromatographic measurement, desflurane concentrations in the 37°C Tyrode superfusate that had been equilibrated for 15 min were 0.42 ± 0.06 mM (n = 3) and 0.91 ± 0.05 mM (n = 4) for 6% and 12% desflurane, respectively. Considering that the Tyrode solution/gas partition coefficient is 0.2 at 37°C,[23] desflurane at 0.42 mM and 0.91 mM correspond to gas phase concentrations of 5.3% (0.89 minimum alveolar concentration [MAC]) and 11.6% (1.93 MAC), respectively. As previously reported, the equilibrated concentrations of isoflurane at 37°C were 0.22 mM for 1.3% and 0.42 mM for 2.5%,[14] corresponding to 1.0% (0.77 MAC) and 1.9% (1.45 MAC) gas phase isoflurane at 37°C, respectively, based on a Tyrode solution/gas partition coefficient of 0.57 at 37°C.[23]

During myocyte experiments at room temperature, desflurane was equilibrated with an external bathing solution in one reservoir by passing 100% O_2 (flow rate: 0.2 l/min) through the desflurane vaporizer for 15 min. Concentrations of 0.78 ± 0.05 mM (n = 3) and 1.23 ± 0.03 mM (n = 3) were measured for 6% and 12% desflurane, respectively. Given that the Tyrode solution/gas partition coefficient is 0.27 at 22°C,[23] the aforementioned desflurane concentrations were equivalent to gas phase concentrations of 7.0% and 11.0%, respectively. An aqueous concentration of 0.78 mM desflurane at 22°C is equivalent to approximately 9.9% desflurane gas phase at 37°C.

Tyramine, phentolamine, propranolol, and reserpine were purchased from the Sigma-Aldrich Chemical Company (St. Louis, MO). To obtain a 1-mg/ml solution of reserpine, reserpine (20 mg) was dissolved in 0.5 ml glacial acetic acid and 1 ml propylene glycol, and then brought to a volume of 20 ml with distilled water. The pH was adjusted to 4.98 with 10N NaOH. Unless otherwise stated, all chemicals were purchased from the Sigma-Aldrich Chemical Company.

Statistical Analysis

Because of the variations in baseline values from one muscle to another, alterations in contractile responses were expressed as a percentage of baseline. In papillary muscle and isolated myocyte experiments, repeated-measures analysis of variance followed by Student-Newman-Keuls test was applied to test for statistically significant differences among the baseline, drug application, and washout period as well as among the stimulation rates. An unpaired *t* test was used to compare the contractile forces between the equianesthetic concentrations of desflurane and isoflurane, and to compare the differences between 6% and 12% concentrations of desflurane. To compare the effects of desflurane among control conditions, groups with adrenoceptor blockade, and reserpine-treated groups, one-way analysis of variance followed by Student-Newman-Keuls test was applied. All results were expressed as mean ± SD. A *P* value less than 0.05 was considered significant.

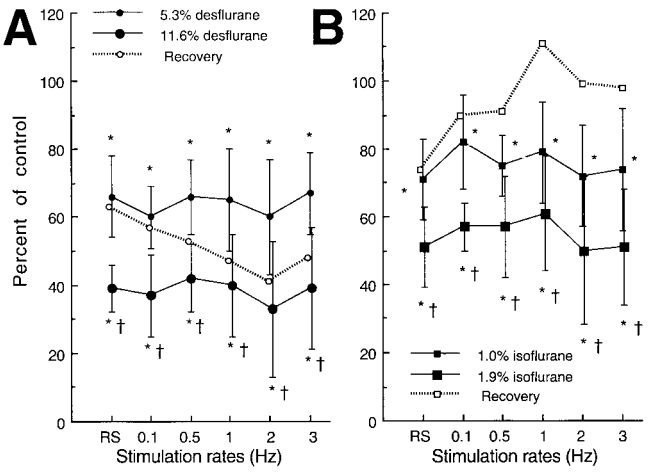

Fig. 1. Effects of equianesthetic concentrations of desflurane (n = 7; *A*) and isoflurane (n = 5; *B*) on myocardial peak force at the indicated stimulation rates in guinea pig papillary muscles. The muscles were successively exposed to 5.3% and 11.6% desflurane or 1.0% and 1.9% isoflurane. *Dotted lines* indicate the 20-min washout after application of 11.6% desflurane or 1.9% isoflurane. *Error bars* indicate SD. * Differences from control (*P* < 0.05). † Differences from 5.3% desflurane or 1.0% isoflurane, respectively (*P* < 0.05). RS = rested state.

Results

Effects on Contractility

Experiments with Modified Standard Tyrode Solution. Desflurane caused concentration-dependent depression of PF to approximately 70% and 40% of baseline from RS to 3-Hz stimulation rates, respectively (n = 7, $P < 0.05$; fig. 1A). Equianesthetic concentrations of isoflurane depressed contractions to approximately 75% and 50% of baseline, respectively (n = 5, $P < 0.05$; fig. 1B). At each stimulation rate, the contractile depression caused by equianesthetic concentrations of desflurane and isoflurane were not different (not significant [NS]). The effects of desflurane and isoflurane on contractile forces did not seem to depend on the stimulation frequencies. Whereas the contractile force recovered to 50–60% of baseline after a 20-min washout of desflurane, equianesthetic concentration of isoflurane exhib-

Table 1. Baseline Values of Peak Force in Modified Standard Tyrode Solution

	RS	0.1 Hz	0.5 Hz	1 Hz	2 Hz	3 Hz
Desflurane (n = 7)	0.25 (0.17)	0.52 (0.35)	0.46 (0.28)	0.62 (0.39)	2.23 (1.66)	3.96 (3.01)
Isoflurane (n = 5)	0.28 (0.20)	0.47 (0.37)	0.39 (0.31)	0.7 (0.54)	2.19 (1.67)	3.92 (3.01)

Results are presented as mean (SD). Peak force (mN/mm^2).
RS = rested state.

ited complete recovery. There was no further recovery after an additional 20-min washout of desflurane (data not shown). The baseline values of PF are shown in table 1.

Tyramine increased the contractile forces to approximately 200% of the baseline from RS to 3-Hz stimulation rates (RS: 179 ± 43%, 0.1 Hz: 168 ± 39%, 0.5 Hz: 186 ± 36%, 1 Hz: 217 ± 70%, 2 Hz: 210 ± 61%, 3 Hz: 162 ± 23%, n = 6). The contractile forces returned to baseline values after washout for 20 min. Treatment with tyramine (30 μM) after α- and β-adrenoceptor blockade (n = 6) or in reserpinized myocardium (n = 6) did not alter the contractile force at each stimulation rate (fig. 2A). Whereas application of α- and β-adrenoceptor blockers did not alter the contractile force at RS and 0.1-Hz stimulation rates, a modest but statistically significant depression to approximately 85% of baseline was observed at 1- to 3-Hz stimulation rates (fig. 2B). Application of desflurane (5.3%) after α- and β-adrenoceptor blockade depressed the contractile force to approximately 50% and 40% of baseline at RS to 1 Hz and higher stimulation rates, respectively (n = 6, $P < 0.05$; fig. 2B). After α- and β-adrenoceptor blockade (n = 8) or in reserpinized myocardium (n = 8), the contractile depression by 5.3% desflurane did not differ from the effects observed under control conditions (fig. 3). To eliminate the contribution of contractile depression by α- and β-adrenoceptor blockade, fractional depression by desflurane was compared with α- and β-blockade baseline values. The baseline values of PF among these three groups are shown in table 2. Similar to the muscles in the absence of pharmacologic sympathetic blockade, partial recovery was observed in the three aforementioned groups at all stimulation rates (data not shown).

Evaluation of Sarcoplasmic Reticulum Function In Situ

Rat Papillary Muscle. Unlike GP muscle, rat muscle SR does not become depleted of Ca^{2+} during rest, but rather accumulates it due to its higher resting intracellular $[Na^+]$,[24,25] resulting in a large RS contraction. Rat papillary muscles also exhibit a negative force–frequency relation, which may be related to hypoxia.[26] Because of the potential for hypoxic alteration, particularly at high stimulation rates, the effect of desflurane (11.6%) was only examined at RS. Alteration of the RS contractile force was not observed in either the presence of desflurane (7.65 ± 2.09 *vs.* 6.99 ± 1.91 mN/mm^2, n = 5, NS) or after a 20-min washout (7.65 ± 2.09 *vs.* 7.19 ± 1.91 mN/mm^2, n = 5, NS).

Experiments with Low-Na^+ (25 mM) Tyrode Solution. In GP myocardium, Ca^{2+} extrusion *via* the Na^+–Ca^{2+} exchange is markedly reduced by low extracellular Na^+ concentration so that Ca^{2+} is accumulated in SR during rest,[19,25] leading to an enhanced RS contraction similar to the behavior of rat myocardium. Contractions in low-Na^+ Tyrode solution require a modest Ca^{2+} current as evidenced by the fact that these contractions are hardly inhibited by nifedipine.[19] Desflurane (11.6%) did not alter the RS contraction (7.34 ± 2.33 *vs.* 6.96 ± 2.03 mN/mm^2, n = 6, NS).

Rapid Cooling Contracture. After a 2-Hz stimulation rate, desflurane (5.3%) markedly depressed the RCC (13 ± 7% of baseline, 3.60 ± 0.52 *vs.* 0.46 ± 0.10

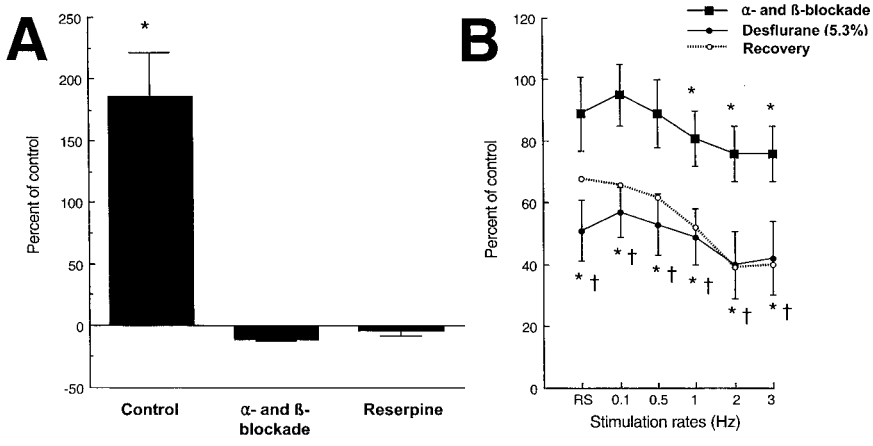

Fig. 2. (*A*) Effects of tyramine (30 μM) on intramyocardial catecholamine release at 1-Hz stimulation rate in guinea pig papillary muscles. In muscles subjected to α- and β-adrenoceptor blockade with phentolamine (1 μM) and propranolol (1 μM) or reserpine, tyramine did not alter the contractile force (n = 6). * Differences from the muscles subjected to α- and β-adrenoceptor blockade or reserpine ($P < 0.05$). (*B*) Effect of 5.3% desflurane–treated muscles subjected to α- and β-adrenoceptor blockade with phentolamine (1 μM) and propranolol (1 μM). *Dotted lines* indicate washout for 20 min. Results are presented as mean ± SD. n = 6/group. * $P < 0.05$ *versus* the baseline. † Differences from the muscles subjected to α- and β-adrenoceptor blockade ($P < 0.05$). RS = rested state.

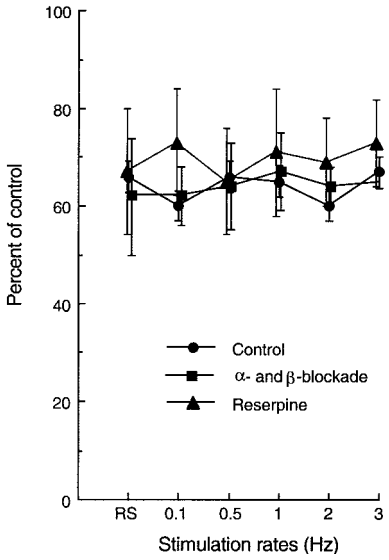

Fig. 3. Effects of 5.3% desflurane on contractile forces in control conditions (n = 7), after α- and β-adrenoceptor blockade with phentolamine (1 μM) and propranolol (1 μM) (n = 8), or after pretreatment of reserpine (n = 8) in guinea pig ventricular myocardium. Results are presented as mean ± SD. RS = rested state.

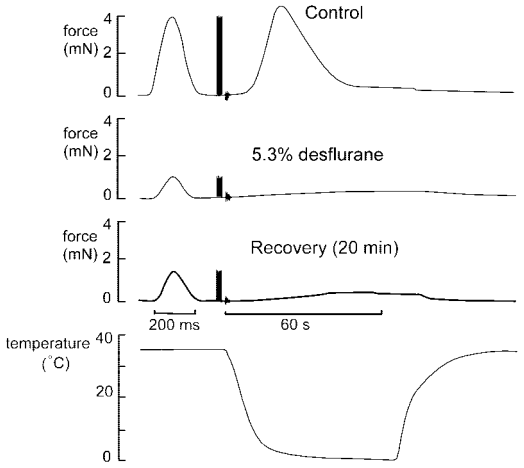

Fig. 4. A typical record of 5.3% desflurane on the rapid cooling contractures in guinea pig myocardium. Steady state contractile force evoked by 2-Hz stimulation rate (shown at high and low chart speed) followed by immediate cooling from 37°C to less than 3°C achieved within 1.5 s, as shown by the temperature measurement in bottom record. Note that while desflurane-induced depression in the electrically evoked contractions showed partial recovery, the effect of desflurane on the rapid cooling contracture was not recovered to baseline value at all.

mN/mm^2, n = 7, $P < 0.05$), and similar depression was shown with 11.6% desflurane (11 ± 7% of baseline, 3.60 ± 0.52 *vs.* 0.36 ± 0.07 mN/mm^2, n = 7, $P < 0.05$). The time to peak contractures could not be determined because the shape of the RCC was almost abolished so that no peak was definable (fig. 4). There was incomplete recovery of the RCC amplitude after a 20-min washout of 5.3% desflurane (28 ± 12% of baseline, 3.60 ± 0.52 *vs.* 0.97 ± 0.18 mN/mm^2, $P < 0.05$; fig. 4).

Experiments with Isoproterenol Stimulation (in 26 mM K^+ Tyrode Solution). With β-adrenergic stimulation in 26 mM K^+ Tyrode solution, the pattern of force after rest and up to 0.5- to 1-Hz stimulation rate consistently demonstrated a distinct early and late phase of force development, defined as dF_E/dt-max and dF_L/dt-max, respectively.[12,13,15,21] Whereas the early peak of the biphasic contraction elicited is activated by Ca^{2+} accumulated during previous depolarizations and released immediately upon rapid depolarization of the membrane, the late peaking force is attributed to the Ca^{2+} that enters the cell during the initial phase of the AP, is taken up into the SR, and is subsequently released late in depolarization.[15,19,21] This late peaking force is depressed by L-type Ca^{2+} channel blockers such as nifedipine.[15,19,21] In contrast, ryanodine decreases the initial force development[15,21] by putting the cardiac Ca^{2+} release channel (RyR2) in a low conductance state and decreasing the SR Ca^{2+} available for immediate release, although the late release is not inhibited.[15] The baseline values of PF, dF_E/dt-max, and dF_L/dt-max are shown in table 3. Desflurane at 5.3% and 11.6% resulted in a marked depression of late force development (5.3%: approximately 40% of baseline, 11.6%: approximately 20% of baseline, n = 7) with a modest to moderate depression of early force development (5.3%: approximately 80% of baseline, 11.6%: approximately 60% of baseline) (figs. 5A–C). After a 20-min washout, near-complete ($P < 0.05$) and complete (NS) recovery of dF_E/dt-max and dF_L/dt-max, respectively, were present.

Electrophysiologic Studies

Papillary Muscle APs. In normal APs, desflurane (11.6%) altered neither the amplitude nor the dV/dt-max at 0.25-Hz stimulation rate, although the APD_{50} and

Table 2. Baseline Values of Peak Force in the Groups Treated with Desflurane, and Pretreated with α and β Blockers or Reserpine Followed by Desflurane in Modified Standard Tyrode Solution

	RS	0.1 Hz	0.5 Hz	1 Hz	2 Hz	3 Hz
Desflurane (n = 7)	0.25 (0.17)	0.52 (0.35)	0.46 (0.28)	0.62 (0.39)	2.23 (1.66)	3.96 (3.01)
α, β Blockers (n = 8)	0.24 (0.15)	0.42 (0.24)	0.43 (0.23)	0.49 (0.24)	1.21 (0.46)	2.22 (0.78)
Reserpine (n = 7)	0.55 (0.13)	1.06 (0.27)	0.99 (0.30)	0.99 (0.35)	2.66 (0.71)	4.89 (0.66)

Results are presented as mean (SD). Peak force (mN/mm^2). There were no significant differences between the groups treated with desflurane and α and β blockers followed by desflurane. The group pretreated with reserpine was not compared with the other two groups because the baseline conditions were different.

RS = rested state.

Table 3. Baseline Values of Main Mechanical Parameters in 26 mM K^+ Tyrode Solution with 0.1 μM Isoproterenol

	RS	0.1 Hz	0.25 Hz	0.5 Hz	1 Hz	2 Hz	3 Hz
PF	3.85 (4.96)	3.80 (4.97)	4.0 (5.49)	4.05 (5.47)	3.62 (5.04)	3.99 (5.30)	3.82 (4.71)
dF_E/dt-max	11.04 (12.17)	13.12 (16.84)	13.27 (15.26)	15.82 (19.26)	29.25 (39.22)	57.43 (68.01)	65.10 (80.72)
dF_L/dt-max	35.74 (46.83)	35.49 (46.88)	37.10 (51.18)	37.10 (51.17)	32.35 (40.49)		

Results are mean (SD) (n = 7).

dF_E/dt-max = maximum rate of early force development ($mN \cdot s^{-1} \cdot mm^{-2}$); dF_L/dt-max = maximum rate of late force development ($mN \cdot s^{-1} \cdot mm^{-2}$); PF = peak force ($mN/mm^2$); RS = rested state.

APD_{90} were prolonged significantly (APD_{50}: 113 ± 7% of baseline, APD_{90}: 111 ± 6% of baseline, n = 6; table 4). No changes in resting membrane potential, which ranged from −87 to −92 mV, were observed. In slow APs, whereas desflurane (11.6%) altered neither the AP amplitude nor the dV/dt-max at 0.25-Hz stimulation rate, the APD_{50} and APD_{90} were also prolonged (APD_{50}: 109 ± 29% of baseline, APD_{90}: 115 ± 15% of baseline, n = 6; table 4). No changes in resting membrane potential, which ranged from −39 to −44 mV, were observed.

Isolated Myocyte Studies.

Inward Rectifier K^+ Current. Using a linear voltage ramp protocol, peak inward I_{KI} at −130 mV was not significantly reduced by 0.78 mM (n = 13) or 1.23 mM desflurane (n = 13) from the control values of −4.74 ± 1.08 and −4.35 ± 1.32 nA, respectively. The peak outward component of I_{KI} elicited at potentials ranging from −60 or −50 mV was also unchanged by 0.78 mM (n = 13) or 1.23 mM desflurane (n = 13) from the control values of 0.29 ± 0.13 and 0.34 ± 0.19 nA, respectively. A typically observed response is shown in figures 6A and B.

Delayed Outward K^+ Current. Whereas I_{KI} did not seem to be significantly reduced by desflurane, the current–voltage relation presented in figure 6 indicates that the outward K^+ current recorded at membrane potentials positive to −20 mV, which primarily represents I_K, was depressed by desflurane. The peak outward I_K assessed at +60 mV was reduced significantly to 63 ± 19% (n = 13, $P < 0.05$) and 58 ± 12% (n = 13, $P < 0.05$) of the baseline values by 0.78 mM and 1.23 mM desflurane from its baseline values of 0.37 ± 0.27 nA and 0.37 ± 0.27 nA, respectively (fig. 6C). Complete recovery was observed after washout (fig. 6A). A more detailed study of time-dependent I_K was performed by measuring the amplitude of I_K at the end of a step depolarization to +80 mV. Desflurane (0.78 mM) reduced the I_K to 57 ± 22% (n = 5, $P < 0.05$) from its baseline value of 1.08 ± 0.31 nA, whereas 1.23 mM desflurane reduced I_K to 61 ± 13% (n = 7, $P < 0.05$) from its baseline value of 0.71 ± 0.12 nA (figs. 7A–D). Washout of desflurane resulted in a complete recovery.

L-type Ca^{2+} Current. At a membrane potential of +10 mV, peak $I_{Ca,L}$ was reduced to 58 ± 6% of baseline (n = 5, $P < 0.05$) by 1.23 mM desflurane from its baseline value of −0.45 ± 0.09 nA (figs. 8A and B). Desflurane (0.78 mM) reduced peak $I_{Ca,L}$ to 77 ± 6% (n = 5, $P < 0.05$) of baseline from its baseline value of −0.4 ± 0.07 nA (fig. 8B). Complete recovery was shown after washout (fig. 8A).

Discussion

The results of the current study demonstrate that desflurane depresses the contractile force in a concentration-dependent manner, similar to the effect of equianesthetic concentration of isoflurane. Myocardial depression by desflurane has been well characterized in isolated atrial[9] and ventricular tissues,[8,10,11] in intact animal studies,[3–6] and in clinical settings.[2,7] Whereas most *in vivo* animal[3,5,6] and human studies[2] have reported similar degree of contractile depression with equianesthetic concentration of desflurane and isoflurane, other *in vivo* animal studies have demonstrated conflicting results showing

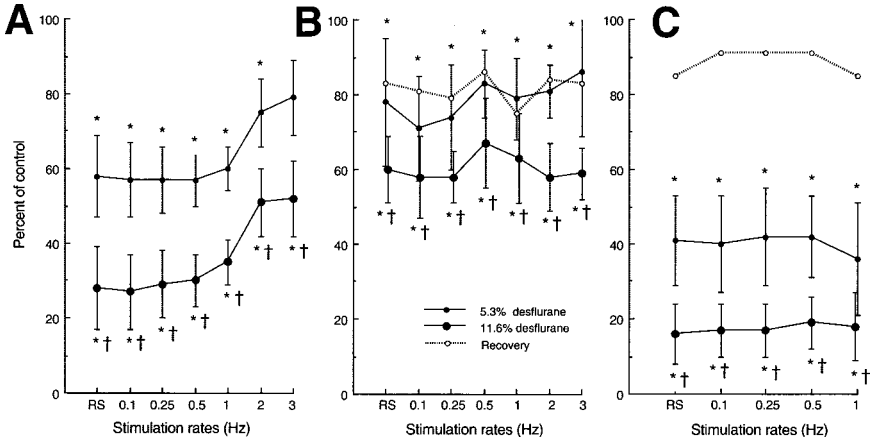

Fig. 5. Effects of desflurane on myocardial force development in 26 mM K^+ Tyrode solution with 0.1 μM isoproterenol in guinea pig ventricular myocardium. (*A*) Effects of 5.3% and 11.6% desflurane on average peak force. Effects of 5.3% and 11.6% desflurane on maximum rate of early, dF_E/dt-max (*B*), and late force development, dF_L/dt-max (*C*), as a function of stimulation rate (n = 7). Muscles were successively exposed to 5.3% and 11.6% desflurane. *Dotted lines* indicate washout for 20 min after application of 11.6% desflurane. *Error bars* indicate SD. * Differences from control ($P < 0.05$). † Differences from 5.3% desflurane ($P < 0.05$). RS = rested state.

Table 4. Effects of Desflurane (11.6%) in Normal and Slow Action Potential Characteristics at 0.25 Hz Stimulation Rate

	Amplitude, mV	APD_{50}, ms	APD_{90}, ms	dV/dt-max, V/s
Normal APs (n = 6)				
Control	128 ± 14	173 ± 16	206 ± 17	126 ± 32
Desflurane	130 ± 15	195 ± 13*	228 ± 15*	123 ± 30
Recovery	131 ± 14	191 ± 6	220 ± 8	132 ± 32
Slow APs (n = 6)				
Control	102 ± 3	165 ± 29	190 ± 32	16 ± 4
Desflurane	104 ± 3	174 ± 31*	215 ± 23*	16 ± 4
Recovery	104 ± 4	175 ± 22	201 ± 28	16 ± 3

Results are presented as mean ± SD. Repeated-measures analysis of variance followed by Student-Newman-Keuls test was used to test for differences among groups.

* $P < 0.05$ *vs.* control.

AP = action potential; APD_{50} and APD_{90} = the duration of the AP at 50% and 90% of repolarization, respectively; dV/dt-max = maximum rate of depolarization of the AP.

greater[27] or less[4] depression than isoflurane. Using a GP heart Langendorff preparation, Bovan *et al.*[8] demonstrated that desflurane caused a slightly greater depression of isovolumic left ventricular pressure than did an equianesthetic concentration of isoflurane, although

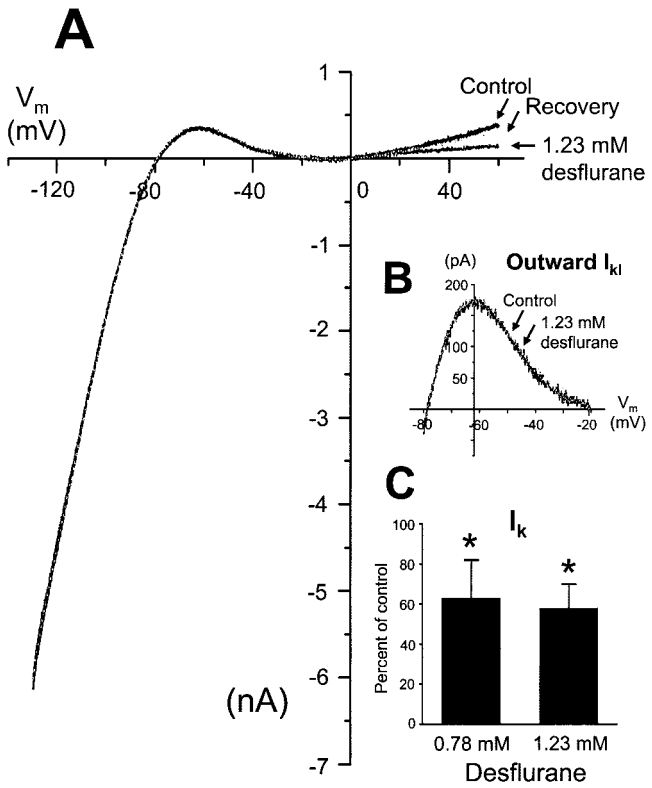

Fig. 6. (*A*) Effects of desflurane on the inward rectifier (I_{KI}) and delayed outward K^+ currents (I_K) in a guinea pig ventricular myocyte. Currents were recorded in response to a linear voltage ramp protocol in which the cells were held at −40 mV before their membrane potential was swept from −130 to +60 mV at a rate of 30 mV/s. A *dotted line* indicates recovery. (*B*) Effects of desflurane on outward component of I_{KI}. (*C*) Effects of 0.78 mM and 1.23 mM desflurane on I_K in guinea pig ventricular myocytes. * $P < 0.05$ *versus* control. *Error bars* indicate SD.

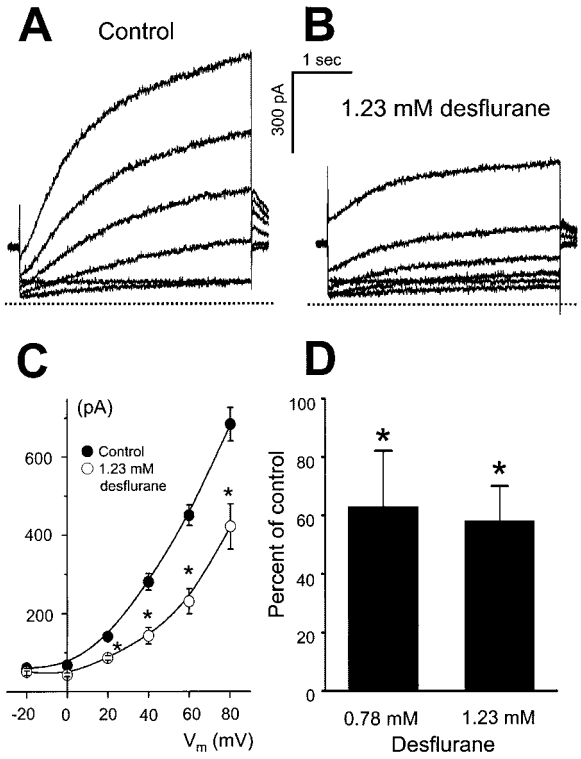

Fig. 7. (*A* and *B*) Effects of desflurane on delayed outward K^+ currents (I_K) in a guinea pig ventricular myocyte. I_K was measured by step depolarizations from −30 to +80 mV from a holding potential of −40 mV in 20-mV increments with 5-s intervals. *Dotted lines* indicate zero current. (*C*) The corresponding current–voltage relations of I_K. * $P < 0.05$ *versus* control. (*D*) Effects of 0.78 mM and 1.23 mM desflurane on I_K. * $P < 0.05$ *versus* control. *Error bars* indicate SD.

greater contractile depression by isoflurane has been reported in rat[10] and hamster myocardium[11] as well as human atrial tissue.[9] The contractile depression observed in this study is compatible with the report by Bovan *et al.*[8] (approximately 40% of control with 11.7% desflurane), and slightly greater than the depression documented by Pagel *et al.*[6] (approximately 75% of baseline by 1 MAC desflurane) in chronically instrumented dogs with pharmacologic blockade of the autonomic nervous system.

A curious observation was the incomplete recovery of normal contractions that we observed after the 20-min washout of desflurane. In previous studies examining isoflurane[12] or sevoflurane,[13] a complete recovery of contractions was observed after a 20-min anesthetic washout. In the current study, identical experiments using isoflurane showed a complete reversal of contractile depression, indicating that there is no time-dependent deterioration in our experimental preparation. To verify the incomplete recovery, we examined four more muscles (control, 11.6% desflurane, and washout) and reconfirmed similar depression (approximately 40%) and recovery (approximately 60%) from RS to 3-Hz stimulation rates. In previous work performed in the same superfused preparation, the depressant effects of propo-

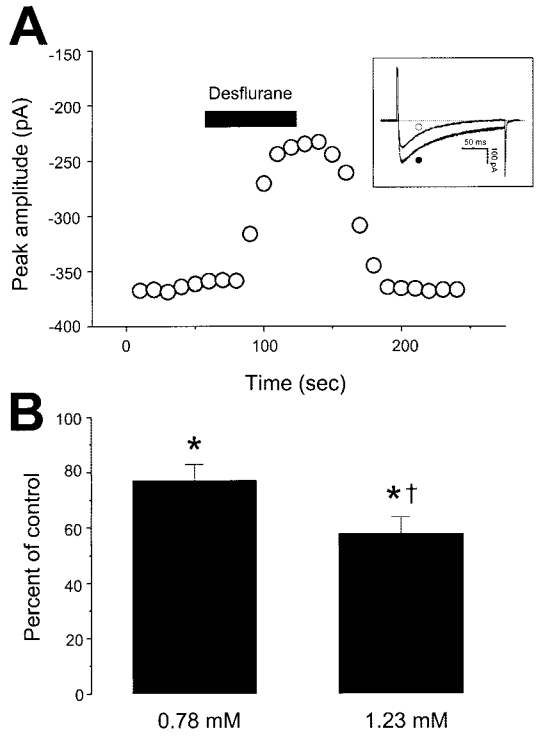

Fig. 8. Effect of desflurane on L-type Ca^{2+} current ($I_{Ca,L}$). (*A*) A representative example of the effect of desflurane on $I_{Ca,L}$ in a guinea pig ventricular myocytes. The *unfilled circles* indicate the peak of an individual current record. The *horizontal bar* indicates the period when desflurane was applied. (*Inset*) An example of individual currents recorded in the presence of 1.23 mM desflurane. *Closed* and *open circles* in the *inset* indicate control and 1.23 mM desflurane, respectively. *Dotted lines* indicate zero current. (*B*) Depression of $I_{Ca,L}$ after application of 0.78 mM and 1.23 mM desflurane. * $P < 0.05$ *versus* control. † $P < 0.05$ *versus* 0.78 mM desflurane. *Error bars* indicate SD.

fol were only partially reversible with washout.[28] Like propofol, desflurane is highly hydrophobic and, once absorbed by the tissue, will diffuse from the tissue and dissolve in the aqueous medium very slowly. In isoproterenol-stimulated muscles in 26 mM K^+ Tyrode solution in the current study, the effects of desflurane seemed to be more reversible on washout. The much more vigorous contractions would increase solution contact and diffusion from the tissue, whereas with weak contractions and minimal motion, diffusion into solution would be restricted by unstirred layers of solution inside and outside the tissue.

In heart muscles, the depolarization-activated release of SR Ca^{2+} is mediated by Ca^{2+} entering the myocyte and triggering the opening of the SR Ca^{2+} release channels (type 2 ryanodine receptors, RyR2), a process termed *Ca^{2+}-induced Ca^{2+} release* (CICR). Over repeated cardiac cycles, depression of $I_{Ca,L}$ will also result in a decrease of Ca^{2+} accumulation in the SR available for subsequent release, consistent with the contractile depression of normal contractions observed with L-type Ca^{2+} channel blockers such as nifedipine.[15] However, when the SR has a very high Ca^{2+} accumulation, such as the RS contraction of rat or GP heart in low Na^+ Tyrode solution, any decrease in $I_{Ca,L}$ seems to be less important because those contractions are minimally depressed by nifedipine.[19] Consequently, the depression of $I_{Ca,L}$ by desflurane in rat or GP hearts in low Na^+ Tyrode solution did not reduce CICR, which has been previously observed for sevoflurane.[13] The lack of depression is likely due to the high concentration of SR luminal Ca^{2+} that seems to prime the RyRs for more complete opening and release.[29] Therefore, even a modest entrance of Ca^{2+} may cause complete RyR activation and Ca^{2+} release from the SR. In addition, the decreased Na^+ gradient may foster "reverse" flow and Ca^{2+} entry through the Na^+–Ca^{2+} exchanger, and this entering Ca^{2+} may contribute to CICR, compensating for depression of $I_{Ca,L}$.[30]

The moderate depression of early tension development observed in our results may be mediated by reduced SR Ca^{2+} content secondary to a reduction of inward Ca^{2+} current by desflurane during previous contractions. However, desflurane, like isoflurane,[12] enflurane,[15] and sevoflurane,[13] markedly reduced late force development in 26 mM K^+ Tyrode solution with 0.1 μM isoproterenol. This depression may be mediated in part by reduction of the inward Ca^{2+} current and/or by the reduction of the late SR Ca^{2+} release. Considering the modest effect on SR Ca^{2+} release in rat and GP myocardium and the reduction of $I_{Ca,L}$ by desflurane in the current results, marked depression of late force development is likely to be mediated by reduction of inward Ca^{2+} current.

Cooling has been shown to increase the open probability of the RyRs,[29,31] and this action likely mediates the Ca^{2+} release that activates the cooling contracture. Desflurane virtually abolished the force induced by rapid cooling, a characteristic that also shared with sevoflurane,[13] isoflurane,[32,33] and enflurane (unpublished results, C. Lynch III, M.D., Ph.D., Charlottesville, Virginia, 1990). However, in the current study, there was only a moderate depression of the 2-Hz contractions by desflurane immediately before cooling, indicating the presence of significant releasable pool of Ca^{2+} in the SR sufficient to elicit depolarization-activated contractile force. The fact that RCC is profoundly inhibited by fluorinated ether anesthetics suggests that the functional properties of the SR Ca^{2+} release channel (RyR2) were altered by such anesthetics while leaving the more physiologic CICR largely intact.[33] The rapid cooling–induced Ca^{2+} release associated with cold cardioplegia is associated with decreased recovery of contractile function *versus* warm cardioplegia.[34] Although this is an interesting experimental observation, the inhibition of rapid cooling–induced Ca^{2+} release by desflurane may have clinical significance. Anesthetic-induced depression of cooling-induced Ca^{2+} release could result in greater recovery of contractile function after cold-induced Ca^{2+} release.

The minimal effect of desflurane on rat cardiac RS contractions as well as on GP myocardium in low Na^+

are consistent with a modest effect on SR Ca^{2+} uptake and its depolarization-activated CICR. These findings suggest that desflurane has a relatively small effect on the amount of Ca^{2+} stored and released, an observation that is consistent with the results of Gueugniaud *et al.*[10] in isolated rat ventricular myocardium. Whereas isoflurane[12] and sevoflurane[13] exhibit effects similar to those of desflurane on SR function, halothane and possibly enflurane stand in contrast with these anesthetic agents by causing a more prominent decrease in initial force development,[12,15] probably by activating the cardiac SR Ca^{2+} release channel and depleting the SR Ca^{2+} store.[35,36]

In GP myocardium, we observed that tyramine concentration-dependently increased the contractile force (data not shown). Further, pretreatment with α and β blockers or reserpine prevented the increase of contractile force by tyramine, indicating that GP myocardium has releasable catecholamine pools. In rat myocardium, Gueugniaud *et al.*[10] demonstrated modest enhancement of contractile force at various concentrations of desflurane. However, the contractile force of rat myocardium after α- and β-adrenoceptor blockade or reserpine administration was significantly depressed by desflurane, suggesting that intramyocardial catecholamine release induced by desflurane counteracted the anesthetic's contractile depression. In contrast, we did not observe any differences for the effects of desflurane on contractile force among control, adrenoceptor-blocked, and reserpine-treated muscles in GP, indicating a clear species-dependent difference in desflurane effects on releasable intramyocardial catecholamines.

To further assess the sympathomimetic effects of desflurane *in vivo* during a rapid increase in desflurane concentration,[37–39] we observed a change in contractility in two muscles stimulated continuously at 0.5 Hz after a rapid increase in desflurane concentrations from 3% (vaporizer setting) to 12% (vaporizer setting). In contrast to the systemic effects observed *in vivo*, this rapid increase of desflurane concentration from 3% to 12% decreased the contractile force similarly (data not shown) to that of a higher desflurane concentration in modified standard Tyrode solution (fig. 1A). None of our results suggest that desflurane induces catecholamine release in the GP ventricular myocardium.

I_K is composed of two different current types: a rapidly activating, inward rectifier current, I_{Kr}, and a slowly activating current, I_{Ks}.[40] In the current study, whole cell voltage clamp experiments indicated that desflurane suppresses the I_K, a property that has been reported for halothane in GP atrial myocytes,[41] and isoflurane[42,43] and sevoflurane in GP ventricular myocytes.[13] Considering the higher voltage used in this study, at which I_{Kr} is usually deactivated, the effects of desflurane primarily represent depression of I_{Ks}, which has been found to be highly sensitive to other inhalational anesthetics such as isoflurane[42,43] and sevoflurane.[44] In contrast, I_{Kr} seems to be less or not sensitive to isoflurane[43,44] and sevoflurane,[44] although it is inhibited by halothane.[45] Further study will be necessary to elucidate the possible effects of desflurane on I_{Kr}.

Although both sevoflurane and isoflurane have been reported to cause significant depression of inward component and enhancement of outward component of I_{KI},[46,47] the actual differences from the baseline values seemed to be modest, suggesting a minimal effect by these anesthetics on I_{KI}. Modest effects on the inward and outward components of I_{KI} by sevoflurane have also been reported in GP ventricular myocytes.[13] We also found that desflurane caused no change in the inward and outward components of I_{KI} in GP ventricular myocytes. The inward rectifier K^+ current is the primary current responsible for maintaining a stable cardiac resting membrane potential near the K^+ equilibrium potential. Inhibition of I_{KI} can result in diastolic depolarization, which in turn can cause increased cardiac excitability[48] and lead to dysrhythmias and abnormal automaticity.[49] The lack of change in the resting membrane potential after application of 0.91 mM desflurane may be attributable to the lack of alteration of I_{KI}.

Our whole cell voltage clamp experiments revealed a concentration-dependent reduction of peak $I_{Ca,L}$ despite the prolongation of AP duration in normal and slow APs. Although inhibition of $I_{Ca,L}$ can lead to a reduction of AP duration, the reduction of I_{Ks} seems to have a greater effect, resulting in AP lengthening. Clinically, significant prolongation of QTc after administration of 1 MAC desflurane has also been reported in adults,[50] and considering that prolongation of AP duration induced by clinically relevant concentrations of desflurane in GP myocytes is most likely due to the suppression of I_K, a similar effect in human myocardium may partially account for the clinical observation of QT prolongation by desflurane.

Overall, the actions of desflurane on the various cellular aspects of Ca^{2+} handling and myocardial contractility seem to be similar to those previously observed in studies of isoflurane and sevoflurane. Contractile depression can be attributed to the depression of Ca^{2+} channel mediated Ca^{2+} influx through the cardiac membrane. The rapid initial release of Ca^{2+} from the SR by depolarization seems to be modestly depressed, although alternative Ca^{2+} release pathways of the RyR Ca^{2+} release channels (cold induced) seem to be markedly depressed. In addition to reduction of $I_{Ca,L}$, a major electrophysiologic effect of desflurane seems to be a depression of the delayed outward K^+ current, which in turn results in an increased AP duration.

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