Summary
The effects of sevoflurane on myocardial contractation and relaxation are poorly understood. Therefore, we studied the effects of equi-anaesthetic concentrations (0.5, 1, 1.5, 2 and 2.5 MAC) of sevoflurane, isoflurane and halothane on inotropic and lusitropic (myocardial relaxation) variables, and post-rest potentiation in rat left ventricular papillary muscles in vitro. Sevoflurane and isoflurane caused comparable concentration-dependent negative inotropic effects which were significantly lower than those induced by halothane (P<0.05). Sevoflurane and isoflurane did not modify lusitropic variables under low or high load, whereas halothane showed a negative lusitropic effect at high concentrations. Halothane suppressed post-rest potentiation, whereas isoflurane and sevoflurane did not. Post-rest recovery was unaffected by halothane, isoflurane or sevoflurane at any concentration. Thus in rat myocardium, sevoflurane and isoflurane caused comparable negative inotropic effects, had no significant lusitropic effects and did not alter post-rest potentiation, suggesting that they did not significantly modify the functions of the sarcoplasmic reticulum. (Br. J. Anaesth. 1998; 80: 621–627)

Keywords: anaesthetics volatile sevoflurane; anaesthetics volatile isoflurane; anaesthetics volatile halothane; heart myocardial function; heart isolated preparation; rat

Sevoflurane is a volatile halogenated anaesthetic characterized by low blood-gas solubility and lack of pungency. These characteristics enable more rapid induction of anaesthesia, more precise adjustment of its effects, faster recovery and administration by mask.¹ The cardiovascular effects of sevoflurane have been studied in vivo in animals²–⁴ and humans.⁵⁻⁷ These studies demonstrated that sevoflurane was less cardiopressant than halothane⁸ and that it induced haemodynamic changes comparable with those observed with isoflurane, except that heart rate was generally lower than with isoflurane.²⁻⁵⁶ Nevertheless, intrinsic myocardial contractility is difficult to assess in vivo because variables used to quantify it are not completely independent of heart rate or load, and because anaesthetic agents markedly modify the activity of the autonomic nervous system. More recently, some in vitro experiments showed that sevoflurane induced electrophysiological changes comparable with those observed with isoflurane.⁸⁻⁹ The negative inotropic effect of sevoflurane has been related to inhibition of trans-sarcolemmal calcium flux.¹⁰ However, there are no data at present comparing the inotropic effects of sevoflurane, isoflurane and halothane. Furthermore, although volatile anaesthetics may impair myocardial relaxation (lusitropy),¹¹ the lusitropic effects of sevoflurane have not been studied in vitro.

In this study, we have compared the inotropic and lusitropic effects of equi-anaesthetic concentrations of sevoflurane, isoflurane and halothane on isolated rat myocardium. We also compared the effects of these anaesthetics on post-rest potentiation of isometric force which provides a useful method of studying the function of the sarcoplasmic reticulum (SR) in a biochemically intact preparation.

Materials and methods
We studied adult Wistar rats (Iffa Credo, France), weighing 250–300 g, according to the recommendations of the Helsinki Declaration and the regulations of the official edict of the French Ministry of Agriculture. After brief anaesthesia with ether, the hearts were removed rapidly and left ventricular papillary muscles were excised carefully and suspended vertically in a 200-ml jacketed reservoir with Krebs–Henseleit bicarbonate buffer solution containing (mmol litre⁻¹): NaCl 118, KCl 4.7, MgSO₄ 1.2, KH₂PO₄ 1.1, NaHCO₃ 25, CaCl₂ 2.5 and glucose 4.5. The Krebs–Henseleit solution was prepared daily with highly purified water (Ecopure, Barnstead/Thermolyne Corporation, Dubuque, IA). The jacketed reservoir was maintained at 29°C with a thermostatic water circulator (Polystat 5HP, Bioblock, Illkirch, France) and continuous monitoring of the temperature of the solution (Pt100 temperature probe, Bioblock). Preparations were field-stimulated at 12 pulses min⁻¹ by two platinum electrodes with rectangular wave pulses of 5-ms
duraion just above threshold. The bathing solution was bubbled with 95% oxygen–5% carbon dioxide, resulting in a pH of 7.40. After a 60-min stabilization period at the initial muscle length at the apex of the length-active isometric tension curve (lmax), papillary muscles recovered their optimal mechanical performance, which remained stable for many hours. Suitable preparations were selected on the basis of the following criteria: length at lmax ≥ 3.0 mm, cross-sectional area (CSA) ≤ 1.20 mm², ratio of resting force to total isometric force (RF/TF) ≤ 0.30 and R1 ≤ 0.85 (R1 = ratio of isotonic shortening and lengthening velocities at a load equal to preload for lmax), as reported previously.12

Control values for each mechanical variable were recorded. Then, the extracellular calcium concentration ([Ca²⁺]o) was decreased from 2.5 to 0.5 mmol litre⁻¹ as rat myocardial contractility approaches a maximum at 2.5 mmol litre⁻¹ and hence it is difficult to quantify inotropic changes without previously decreasing [Ca²⁺]o.13 Moreover, a decrease in [Ca²⁺]o is necessary to study post-rest potentiation.12 To ensure that the inotropic reserve was comparable between groups, suitable preparations were selected as follows: the decrease in active isometric force and maximum shortening velocity should be within 40–75% and 60–80% of control values at [Ca²⁺]o, 2.5 mmol litre⁻¹, respectively. Thereafter, we studied the effects of equi-anaesthetic concentrations (0.5, 1.0, 1.5, 2.0, 2.5 minimum alveolar concentration (MAC) of halothane (n = 8), isoflurane (n = 8) and sevoflurane (n = 8) on mechanical variables, and on post-rest potentiation.

Halothane (Fluotec 3, Cyprane Ltd, Keighley, UK), isoflurane (Fortec 3, Cyprane Ltd) and sevoflurane (Sevotec 3, Ohmeda, West Yorkshire, UK) were delivered with specific vaporizers using carbogen as the carrier gas. The gas mixture was bubbled continuously in the bathing solution. To minimize evaporation of anaesthetic vapours, the jacketed reservoir was sealed with a thin paraffin sheet (Parafilm M, American National Can, Greenwich, CT, USA), as described previously.11 Anaesthetic concentrations in the gas phase were measured continuously using an infrared calibrated analyser (Capnomac, Datex, Helsinki, Finland). The MAC values of halothane, isoflurane and sevoflurane in adult rats at 29°C were calculated as 0.6%, 0.8% and 1.44 vol%, respectively.15–15 These concentrations in the gas phase correspond to a concentration of approximately 0.25 mmol litre⁻¹ in the bathing solution. The concentrations tested were equivalent to 0.5, 1, 1.5, 2 and 2.5 MAC. A 20-min period of equilibration was allowed between each anaesthetic concentration and recording of mechanical variables.

ELECTROMAGNETIC LEVER SYSTEM AND RECORDING

The electromagnetic lever system has been described previously.11 Briefly, the load applied to the muscle was determined using a servo mechanism-controlled current through the coil of an electromagnet. Muscular shortening induced displacement of the lever, which modulated the light intensity of a photodiode transducer. All analyses were made from digital records of force and length obtained with a computer, as described previously.11

MECHANICAL VARIABLES

Conventional mechanical variables at lmax were calculated from three twitches. The first twitch was isotonic and was loaded with the preload corresponding to lmax. The second twitch was abruptly clamped to zero load just after the electrical stimulus; the muscle was released from preload to zero load with critical damping in order to slow the first and rapid shortening overshoot resulting from the recoil of series passive elastic components, as reported previously; the maximum unloaded shortening velocity (vmax) was determined from this twitch. The third twitch was fully isometric at lmax.

The mechanical variables characterizing the contraction and relaxation phases, and the coupling between contraction and relaxation are defined below (fig. 1).

Contraction phase

We determined vmax using the zero load clamp technique; maximum shortening velocity (maxv) of the twitch with preload only; maximum isometric active force normalized per cross-sectional area (AF); and peak of the positive force derivative normalized per cross-sectional area (+dF/dt). vmax and AF tested the inotropic state under low and high loads, respectively.

Relaxation phase

We determined maximum lengthening velocity of the twitch with preload only (maxL) and the peak of the negative force derivative at lmax normalized per

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**Table 1** Control values (mean (SD)) of the main mechanical variables in papillary muscle strips.

<table>
<thead>
<tr>
<th></th>
<th>Halothane group (n=8)</th>
<th>Isoflurane group (n=8)</th>
<th>Sevoflurane group (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>v max (m/s)</td>
<td>2.26 (0.48)</td>
<td>2.15 (0.28)</td>
<td>1.93 (0.30)</td>
</tr>
<tr>
<td>AF (mN mm⁻²)</td>
<td>40 (10)</td>
<td>42 (16)</td>
<td>34 (16)</td>
</tr>
<tr>
<td>R1</td>
<td>0.63 (0.12)</td>
<td>0.70 (0.10)</td>
<td>0.72 (0.19)</td>
</tr>
<tr>
<td>R2</td>
<td>1.77 (0.22)</td>
<td>1.77 (0.16)</td>
<td>1.61 (0.12)</td>
</tr>
</tbody>
</table>
Data are mean isometric active force normalized per cross-sectional area (AF).

The contraction–relaxation coupling variables have been validated recently as indexes of myocardial lusitropy.10

**Contraction–relaxation coupling**

Coefficient $R_1 (\text{max}_c/\text{max}_r)$ describes the coupling between contraction and relaxation under low load and thus reflects myocardial lusitropy in a manner which is independent of inotropic changes. In contrast with both max$_c$ and max$_r$, $R_1$ is not significantly modified by major inotropic changes.11 Under isotonic conditions, the amplitude of sarcomere shortening is greater than that observed under isometric conditions.18 Because of the lower sensitivity of myofilament for calcium when cardiac muscle is markedly shortened under low load, relaxation proceeds more rapidly than contraction, apparently because of rapid uptake of calcium by the SR. Thus, in rat myocardium, $R_1$ describes the SR uptake function. Coefficient $R_2 (= +dF.dr^{-1}/−dF.dr^{-1})$ describes the coupling between contraction and relaxation under high load and thus the lusitropic state under high load in a manner which is less dependent on inotropic changes.11 When the muscle contracts isometrically, sarcomeres shorten very little.19 Because of the higher sensitivity of myofilament for calcium, the relaxation time course is determined by calcium unbinding from troponin C rather than by calcium sequestration by the SR. Thus, $R_2$ (contraction–relaxation coupling under heavy load) indirectly reflects myofilament calcium sensitivity.11,17

The contraction–relaxation coupling variables $R_1$ and $R_2$ have been validated recently as indexes of myocardial lusitropy.20

**POST-REST POTENTIATION**

Recovery of a stable, reproducible isometric contraction after a rest interval (1 min) was studied to identify the effects of volatile anaesthetics on SR function. In the rat, at rest, SR accumulates calcium in addition to that accumulated under regular stimulation, and the force of the first beat after the rest interval (B1) is greater than that of the last beat before the rest interval (B0). In rat heart muscle, post-rest potentiation is highly dependent on SR calcium release.21 During stimulation of post-rest recovery (B1, B2, B3...), the SR-dependent portion of the activator calcium decreases somewhat towards steady state, which is reached in a few beats. Therefore, comparison of the effects of halothane, isoflurane and sevoflurane on post-rest-potentiated contraction may provide insight into the differential effects of volatile anaesthetics on SR function in a biochemically intact preparation. As described previously, maximal AF during post-rest recovery was studied at [Ca$^{2+}$]o 0.5 mmol litre$^{-1}$, after a rest period of 1-min and at a stimulation frequency of 12 pulses min$^{-1}$.12 The rate constant, $\tau$, of the exponential decay of AF was determined, as described previously.12 $\tau$ is the number of beats required for post-rest contraction to decay to one-tenth of its maximum (B1); it is assumed to represent the time required for the SR to reset itself, and was therefore used to test SR function.22

At the end of the study, muscle cross-sectional area was calculated from the length and weight of papillary muscle, assuming a density of 1. Shortening and lengthening velocities were expressed in max $s^{-1}$, force in mN mm$^{-2}$ and force derivative in mN mm$^{-2}$ s$^{-1}$.

**STATISTICAL ANALYSIS**

Data are expressed as mean (SD). Control values between groups were compared by analysis of variance. Comparison of several means was performed using analysis of variance and Newman–Keuls test. Beat-to-beat decay of active isometric force during post-rest recovery was plotted against the number of beats and fitted to an exponential curve, and regression was performed using the least squares method, as described previously.12 All $P$
values were two-tailed, and \( P < 0.05 \) was required to reject the null hypothesis. Statistical analysis was performed on a computer using NCSS 6.0 software (Statistical Solutions Ltd, Cork, Ireland).

**Results**

We studied 24 left ventricular papillary muscles. There were no significant differences in control values for \( \ell \max \), CSA, RF/TF or contraction–relaxation coupling under low load \((R_1)\) at \([\text{Ca}^{2+}]_o\) 2.5 mmol litre\(^{-1}\) between groups. Mean values for these variables were as follows: \( \ell \max \) 4.9 (1.3) mm; CSA 0.70 (0.05) mm\(^2\); RF/TF 0.11 (0.05); and \( R_1 \) 0.68 (0.08). A decrease in contractility was observed as \([\text{Ca}^{2+}]_o\) was decreased: \( \varepsilon \)max and AF were 75 (11) % and 50 (11) % of the value at \([\text{Ca}^{2+}]_o\) 2.5 mmol litre\(^{-1}\), respectively. These results were consistent with previous reports.\(^{11,12}\) The control values of the main mechanical variables of papillary muscles in each group are reported in table 1.

**INOTROPIC EFFECTS**

Halothane, isoflurane and sevoflurane caused concentration-dependent negative inotropic effects, as shown by the decrease in \( \varepsilon \)max and AF (fig. 2). Halothane was the more potent negative inotropic agent, whereas isoflurane and sevoflurane induced comparable negative inotropic effects (fig. 2). The maximum decrease in AF (15 (9) % of control values) measured at 2.5 MAC of halothane was significantly different from that measured at 2.5 MAC of isoflurane and sevoflurane (64 (14) % and 67 (22) % of control values, respectively).

**LUSITROPIC EFFECTS**

Halothane at 2.5 MAC significantly increased \( R_1 \), indicating a negative lusitropic effect under low load (161 (57) % of control values; \( P < 0.05 \)) (fig. 3). Halothane induced a slight concentration-dependent decrease in \( R_2 \). However, it should be noted that the magnitude of this effect was equivalent to that observed by decreasing \([\text{Ca}^{2+}]_o\) from 0.50 to 0.25 mmol litre\(^{-1}\) (89 (6) % of control values; ns).\(^{11}\) Isoflurane and sevoflurane induced a slight comparable increase in \( R_1 \) (fig. 3). Isoflurane and sevoflurane did not significantly modify \( R_2 \) at any concentration (fig. 3).

**EFFECTS ON POST-REST POTENTIATION AND RECOVERY**

Post-rest potentiation \((B_1/B_0)\) of AF did not differ between groups (137 (10) % in the halothane group, 134 (6) % in the isoflurane group and 136 (10) % in the sevoflurane group). Halothane induced a dose-dependent decrease in post-rest potentiation (fig. 4). At 2.5 MAC, AF developed by the first contraction after the rest period was only 111 (10)% of AF developed before the rest period. Isoflurane did not significantly modify post-rest potentiation of AF at any concentration (fig. 4). Sevoflurane increased post-rest potentiation in a concentration-dependent manner. 
Table 2 Values (mean (SD)) for the rate constant (τ) of the exponential decay in active isometric force (AF) after post-rest potentiation. τ= number of beats required for post-rest contraction to decay to one-tenth of its maximum (B1). No significant differences between groups

<table>
<thead>
<tr>
<th></th>
<th>Halothane group (n=8)</th>
<th>Isoflurane group (n=8)</th>
<th>Sevoflurane group (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.1 (0.7)</td>
<td>3.3 (0.5)</td>
<td>3.3 (0.6)</td>
</tr>
<tr>
<td>0.5 MAC</td>
<td>3.1 (0.3)</td>
<td>3.0 (0.5)</td>
<td>3.4 (0.6)</td>
</tr>
<tr>
<td>1 MAC</td>
<td>3.1 (0.4)</td>
<td>3.2 (0.6)</td>
<td>3.3 (0.7)</td>
</tr>
<tr>
<td>1.5 MAC</td>
<td>3.4 (0.7)</td>
<td>3.5 (0.6)</td>
<td>3.4 (0.7)</td>
</tr>
<tr>
<td>2 MAC</td>
<td>3.7 (0.4)</td>
<td>3.5 (0.5)</td>
<td>3.3 (0.7)</td>
</tr>
<tr>
<td>2.5 MAC</td>
<td>3.9 (1.0)</td>
<td>3.6 (0.3)</td>
<td>3.4 (0.8)</td>
</tr>
</tbody>
</table>

manner (fig. 4). Halothane, isoflurane and sevoflurane did not modify post-rest recovery, as assessed by τ, at any concentration (table 2).

Discussion

We have compared the direct myocardial effects of a wide range of equi-anaesthetic concentrations of sevoflurane, isoflurane and halothane. We showed that, in isolated rat myocardium, the negative inotropic effects of sevoflurane and isoflurane were comparable and significantly lower than those caused by halothane. Whereas halothane induced a marked negative lusitropic effect under low load, sevoflurane and isoflurane did not. In addition, sevoflurane and isoflurane did not alter post-rest potentiation, suggesting that they had no significant effects on SR function.

The cardiovascular effects of sevoflurane were first studied in vivo in pigs by Manohar and Parks in 1984. These authors reported a dose-dependent decrease in cardiac output and mean arterial pressure, without significant changes in heart rate. Sevoflurane and isoflurane caused almost comparable in vivo effects on systemic and regional haemodynamic variables in rats and dogs. However, these studies did not assess intrinsic myocardial contractility. Harkin and colleagues studied the inotropic effects of several concentrations of sevoflurane in chronically instrumented dogs. However, sevoflurane was studied alone, and variables used to assess myocardial contractility were not completely independent of preload, afterload or heart rate. Moreover, the effects of sevoflurane on autonomic nervous system activity could not be excluded completely. Two clinical studies comparing the cardiovascular effects of isoflurane and sevoflurane in healthy patients or volunteers concluded that isoflurane or sevoflurane anaesthesia induced similar cardiovascular effects. However, these studies may suffer from the same criticisms concerning the relationship between haemodynamic variables and myocardial inotropic or lusitropic state.

Recently, in an in vitro study compared the effects of equimolar concentrations of sevoflurane and isoflurane on isolated spontaneous beating guinea pig hearts. Although this study showed that sevoflurane and isoflurane produced equivalent chronotropic and coronary vasodilatory effects, it should be noted that heart rate was not maintained constant, and left ventricular pressure is not considered a good index of the inotropic status of the myocardium.

Our study demonstrated that sevoflurane and isoflurane induced an equivalent concentration-dependent negative inotropic effect (fig. 2). Halothane caused a greater decrease in \( r_{\text{max}} \) and AF than isoflurane or sevoflurane (fig. 2). When MAC values are corrected according to temperature, the negative inotropic effects of halothane and isoflurane corresponded to those reported previously. The main mechanisms by which volatile anaesthetics cause myocardial depression are profound alteration of the main cellular components involved in intracellular calcium homeostasis. The differences in myocardial depressant effects of volatile anaesthetics, namely halothane and isoflurane, may be explained by their differential effects on calcium inward currents \( (I_{\text{Ca}}) \) and SR function.

In isolated myocytes, sevoflurane decreased the plateau and shortened the duration of the action potential mainly by inhibition of \( I_{\text{Ca}} \) presumably via L-type Ca\(^{2+}\) channels. Furthermore, Hirota and colleagues suggested that sevoflurane and isoflurane reduced the time constant of Ca\(^{2+}\) current inactivation by enhancing the probability of closing the inactivation gate. In isolated rat cardiac cell suspensions, halothane, but not isoflurane, depleted the SR of Ca\(^{2+}\). This effect may be related to the fact that clinically relevant concentrations of halothane, but not isoflurane, gate the cardiac SR Ca\(^{2+}\) release channel into the open state. The effects of sevoflurane on SR function are unknown at present, but it could be suggested, based on their equivalent inotropic and lusitropic effects, that they may be similar to those of isoflurane.

It has been shown that in rat myocardium the SR accounts almost entirely for calcium removal from the cytoplasm during the relaxation phase. It describes the lusitropic state under low load and reflects rapid uptake of calcium by the SR. We showed that the increase in \( r_{\text{Ca}} \) caused by halothane was greater than those caused by sevoflurane and isoflurane (fig. 3). Our results on the negative lusitropic effects of halothane under low load are in agreement with those reported previously. The lack of negative lusitropic effects of isoflurane and sevoflurane under low load was observed even at high anaesthetic concentrations and agrees with a previous study in chronically instrumented dogs.

However, our results suggest that sevoflurane did not significantly modify calcium uptake by the SR. We showed that halothane decreased post-rest potentiation, whereas isoflurane and sevoflurane did not (fig. 4). This is in agreement with our knowledge of the effects of halothane on SR function. It has been shown that halothane inhibits SR calcium uptake and release and depletes the SR of calcium. Although isoflurane may inhibit cardiac Ca\(^{2+}\) ATPase, it did not alter SR calcium content and release. Hence, post-rest potentiation provides a useful tool for examining complex underlying cellular processes, such as SR calcium release in intact cardiac muscle. Sevoflurane caused a slight increase in post-rest potentiation. This effect requires further study to elucidate the precise underlying cellular processes. Two hypotheses can be raised: first, sevoflurane increases the amount of calcium slowly accumulated in the SR during the rest period, and second, it increases calcium release from the SR. Halothane, isoflurane and sevoflurane did not affect post-rest recovery, assessed by the rate constant, τ, of the SR.
exponential decay of AF (table 2). This suggests that halogenated anaesthetics do not significantly alter the recirculation fraction of calcium within the SR.\(^2\)\(^2\)\(^2\)

R2 tested the lusitropic state under high load and thus could indirectly reflect myofilament calcium sensitivity. Our results showed that sevoflurane and isoflurane did not significantly modify R2 (fig. 3), suggesting that they did not induce a lusitropic effect under high load and therefore did not modify myofilament calcium sensitivity. High concentrations of halothane cause a slight decrease in R2 but this was not greater than that observed by decreasing calcium to obtain a comparable negative inotropic effect.\(^1\)\(^1\) Indeed, calcium per se modulates myofilament calcium sensitivity, according to the cooperativity concept.\(^3\)\(^2\)\(^2\) These results may be clinically important as diastolic function significantly influences overall cardiac performance. Indeed, our results suggest that sevoflurane, at clinically relevant concentrations, does not significantly modify myocardial relaxation.

The following points must be considered in the assessment of the clinical relevance of our results. First, as this study was conducted in vitro, it dealt only with intrinsic myocardial contractility and did not take into account the vasodilatory effects of volatile anaesthetics or their influences on sympathetic nervous system tone in vivo. Second, this study was carried out at 29°C and at a low-stimulation frequency; however, papillary muscles must be studied at this temperature because the stability of mechanical variables is low at 37°C, and at a low frequency because high-stimulation frequency may induce core hypoxia.\(^2\)\(^3\)\(^3\) Third, it was performed on rat myocardium, which differs from human myocardium. In rat myocardium, contractility is high, calcium-induced calcium release from the SR is highly developed and myosin isoforms are predominantly of the V1 type. Nevertheless, the effects of volatile anaesthetics on the myocardium appear to be similar from one species to another.\(^2\)\(^3\)\(^3\)

In summary, in isolated rat myocardium, sevoflurane caused a moderate negative inotropic effect equivalent to that of isoflurane and lower than that of halothane. In contrast with halothane, sevoflurane and isoflurane had no significant lusitropic effects and did not modify post-rest potentiation or recovery, suggesting that they did not significantly alter SR function.

Acknowledgements

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Effects of sevoflurane, isoflurane and halothane on rat myocardium


