Interaction of Halogenated Anesthetics with Dobutamine in Rat Myocardium

Pierre-Yves Gueguenlaud, M.D., Ph.D,*, Jean-Luc Hanouz, M.D.,† Jean-Marc Martino, M.D.,‡ Yves Lecarpentier, M.D., Ph.D,§ Pierre Coriat, M.D.,∥ Bruno Riou, M.D., Ph.D.#

**Background:** Halogenated anesthetics potentiate the positive inotropic effects of α- and β-adrenoceptor stimulations, but their interactions with dobutamine remain unknown.

**Methods:** The effects of halothane, isoflurane, sevoflurane, and desflurane (1 and 2 minimum alveolar concentration) on the inotropic responses induced by dobutamine (10⁻²–10⁻³ m勀) were studied in rat left ventricular papillary muscles in vitro. Inotropic effects were studied under low (isotropy) and high (isometry) loads. The authors also studied the lusitropic effects in isotonic (R1) and isometric (R2) conditions. Data are the mean percentage of baseline ± SD.

**Results:** Dobutamine induced a positive inotropic effect (active isometric force: 185 ± 36%, P < 0.001) and a positive lusitropic effect under low load (R1: 78 ± 9%, P < 0.001), but not under high load (R2: 95 ± 21%, not significant). Halothane, isoflurane, and sevoflurane did not modify the positive inotropic effect of dobutamine. Even in the presence of α-adrenoceptor blockade, isoflurane did not potentiate the positive inotropic effect of dobutamine. Desflurane significantly enhanced the positive inotropic effect of dobutamine (active isometric force: 239 ± 35%, P < 0.001), but this potentiation was abolished by pretreatment with reserpine. In contrast to halothane, isoflurane, sevoflurane, and desflurane did not significantly modify the lusitropic effects of dobutamine.

**Conclusions:** Halogenated anesthetics, except desflurane, did not modify the positive inotropic effects of dobutamine. Desflurane enhanced the positive inotropic effect of dobutamine, but this effect was related to the desflurane-induced release in intramyocardial catecholamine stores. (Key words: Catecholamines; contractility; heart.)

Although halogenated anesthetics induce negative inotropic effects,¹ they have been shown to enhance the positive inotropic effects of α- and β-adrenoceptor stimulations in isolated myocardium.² Five investigators have suggested that this potentiation is related to the interaction of halogenated agents with G proteins coupled to the adrenoceptors.²⁻³ Schmidt et al.⁴ have shown that halothane decreases the function of the inhibitory G proteins, probably by interfering with the effects of α or β subunits on the effector. The degree of potentiation appears to be similar among halothane, isoflurane, and sevoflurane.²⁻³ but information is lacking for desflurane. Dobutamine is a widely used adrenergic agent that has been advocated in the treatment of cardiac failure⁵ and septic shock⁶ and has been shown to improve the balance between oxygen demand and oxygen delivery, metabolic status, and regional blood flow in critically ill patients.⁷⁻⁹ Dobutamine exhibits potent β-agonist properties but also stimulates α adrenoceptors.¹⁰ Because only pure α- or β-adrenoceptor stimulations were studied before, and because complex interactions exist between α- and β-adrenoceptor stimulations,¹¹ we were interested in the potential interaction between halogenated anesthetic agents and dobutamine. Therefore, we conducted an in vitro study of the interactions of the main halogenated anesthetics (halothane, isoflurane,
sevoflurane, and desflurane) with dobutamine in isolated rat myocardium.

**Materials and Methods**

We used adult Wistar rats that weighed 250-300 g. Care of the animals conformed to the recommendations of the Helsinki Declaration, and the study was performed in accordance with the regulations of the official edict of the French Ministry of Agriculture.

**Experimental Protocol**

As previously reported, left ventricular papillary muscles were studied in Krebs-Henseleit bicarbonate buffer solution (118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 1.1 mM KH2PO4, 25 mM NaHCO3, 2.5 mM CaCl2, and 4.5 mM glucose) maintained at 29°C. Preparations were field stimulated at 12 pulses/min by two platinum electrodes with rectangular wave pulses lasting 5 ms just above threshold. The bathing solution was bubbled with 95% oxygen and 5% carbon dioxide, resulting in a pH of 7.4. 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 functional performance. The extracellular calcium concentration ([Ca2+]o) was decreased from 2.5 mM to 0.5 mM because rat myocardial contractility is at its nearly maximum value at 2.5 mM. Because there are important differences in baseline values from one muscle to another, isotropic responses were expressed as a percentage of baseline values (i.e., after exposure of halogenated anesthetics), as previously reported. We found that decreasing contractility by reducing the extracellular calcium concentration does not induce any potentialization of α- and β-adrenoceptor stimulations.

Thus, in control groups (n = 10 in each group) we studied the effects of increasing concentrations (10^-8 - 10^-3 M) of dobutamine (Lilly, Indianapolis, IN) in a cumulative manner. The total volume of drugs did not exceed 2% of the bath volume. The isotropic and lusitropic responses were recorded 10 min after each dose was added to the bathing solution. We studied the same concentrations of dobutamine in separate groups of papillary muscles previously exposed to equianesthetic concentrations of four halogenated anesthetic agents (halothane, isoflurane, sevoflurane, or desflurane) at 1 (n = 10 in each group) or 2 (n = 6 in each group) minimum alveolar concentration (MAC). We also compared the effects of dobutamine with those of isoproterenol (10^-8 - 10^-4 M) in the presence of phenolamine (10^-6 M) and phenylephrine (10^-8 - 10^-4 M) in presence of propranolol (10^-6 M).

Because desflurane releases intramyocardial catecholamine stores in rat myocardium, the effects of dobutamine in the presence of desflurane were also tested in rats pretreated with reserpine (4 mg/kg injected intraperitoneally 24 h before killing; n = 10). Finally, we studied the effects of dobutamine in the presence of MAC isoflurane and α-adrenoceptor blockade (10^-6 M phenolamine; n = 8) and compared them with those of dobutamine in the presence of α-adrenoceptor blockade (n = 8).

**Volatile Anesthetic Agent Administration**

Halothane (Fluotec 3; Cyprane Ltd., Keighley, UK), isoflurane (Fortec 5; Cyprane Ltd.), sevoflurane (Sevotec 3; Ohmeda, West Yorkshire, UK), and desflurane (Devapar; Dräger, Lubeck, Germany) were added to the carbon dioxide-oxygen mixture using calibrated vaporizers. The gas mixture bubbled continuously in the bathing solution. To minimize the evaporation of halogenated anesthetics, the jacketed reservoir was covered with a thin paraffin sheet. Anesthetic concentrations in the gas phase were measured continuously using an infrared calibrated analyzer (Artema MM206; Taema, Antony, France). The following concentrations were used: halothane, 0.6 and 1.2 vol%; isoflurane, 0.8 and 1.6 vol%; sevoflurane, 1.4 and 2.8 vol%; and desflurane, 3.7 and 7.5 vol%. These concentrations are equivalent to 1 and 2 MAC in the adult rat at 29°C, respectively. A 20-min equilibration period was allowed before baseline values of mechanical parameters were recorded.

**Electromagnetic Lever System and Recording**

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

**Mechanical Parameters**

Conventional mechanical parameters at Lmax were calculated from three twitches. The first twitch was isotonic and was loaded with the preload corresponding to Lmax; we determined maximum shortening (cmax Vc) and...
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lengthening ($V_r$) velocities from this twitch. The second twitch was clamped abruptly to zero-load just after the electric stimulus, with a critical damping to slow the first and rapid shortening overshoot resulting from the recoil of series passive elastic components\(^6\), the maximum unloaded shortening velocity ($V_{max}$) was determined from this twitch. The third twitch was fully isometric at $I_{max}$; the maximum isometric active force normalized per cross-sectional area (active isometric force [AF]), and the peak of the positive (+dF/dt) and the negative (−dF/dt) force derivatives at $I_{max}$ normalized per cross-sectional area were determined from this twitch. $V_{max}$ and AF tested the inotropic state under low (isotony) and high (isometry) loads, respectively. Because changes in the contraction phase induce coordinated changes in the relaxation phase, $V_r$ and −dF/dt cannot assess lusitropy, and thus variations in contraction and relaxation must be considered simultaneously to quantify drug-induced changes in lusitropy.\(^1\) The coefficient $R_1 = V_r \frac{V_r}{V_{max}V_r}$ evaluated coupling of the lusitropy under low load.\(^1\) During isotonic conditions, the amplitude of sarcomere shortening is greater than that observed during isometric conditions.\(^8\) Because of the lower sensitivity of myofilaments for calcium when the cardiac muscle is markedly shortened under low load, relaxation proceeds more rapidly than contraction, apparently because of the rapid uptake of calcium by the sarcoplasmic reticulum.\(^9\) Thus, in rat myocardium, $R_1$ tests sarcomplasmic reticulum uptake function.\(^3,4\) The coefficient $R_2 = \frac{+dF \cdot dt^{-1}}{-dF \cdot dt^{-1}}$ evaluated the lusitropy under high load. When the muscle contracts isometrically, sarcomeres shorten very little.\(^8\) Because of the higher sensitivity of myofilaments for calcium,\(^9\) the time course of relaxation is determined by calcium unbinding from troponin C rather than by calcium sequestration by the sarcoplasmic reticulum. Thus, $R_2$ indirectly reflects myofilament calcium sensitivity.\(^1\) A decrease in $R_1$ or $R_2$ indicates a positive lusitropic effect.

**Results**

We studied 114 left ventricular papillary muscles. The mean $I_{max}$ was 5.2 ± 0.6 mm; the mean cross-sectional area was 0.67 ± 0.06 mm²; the mean ratio of resting force to total force was 0.15 ± 0.04; the mean contraction–relaxation coupling under low load (R1) was 0.69 ± 0.03, at a $[Ca^{2+}]_o$ of 2.5 mm; and no significant differences were noted among the groups. Decreases in $V_{max}$ (69 ± 6%) and AF (57 ± 7%) were observed as $[Ca^{2+}]_o$ was decreased from 2.5 to 0.5 mm, as previously reported.\(^2,3\) Even after exposure to halogenated anesthetics, no significant differences in baseline values were noted between groups (table 1).

In the control group, dobutamine induced a significant positive inotropic effect in isotonic and isometric conditions. Peak enhancement of $V_{max}$ and AF occurred at $10^{-3}$ M dobutamine (table 2). Furthermore, dobutamine induced a significant positive lusitropic effect under low load but not under high load (table 2). When a higher ($10^{-3}$ M) concentration of dobutamine was tested, we observed a decrease in the positive inotropic effect (AF: 141 ± 48% of baseline) compared with $10^{-4}$ M and the disappearance of the positive lusitropic effect under low load (R1: 100 ± 21% of baseline, not significant), which suggested a toxic effect, as previously reported.\(^9\) Consequently, the concentration–response curves were analyzed between $10^{-8}$ and $10^{-4}$ M. The magnitude of the positive inotropic effect of dobutamine was comparable to that of isoproterenol and significantly greater than that of phenylephrine (table 2). Nevertheless, the concentration–response curve of dobutamine was shifted to the right; that is, it was less potent compared with that of isoproterenol (AF, C50: 3.4 ± 2.3 vs. 0.5 ± 0.4 μM, $P < 0.05$). Dobutamine did not induce any significant lusitropic effect under high load (table 2).

Figure 1 shows the absolute values of AF recorded in response to increasing concentrations of dobutamine, during control conditions, and in the presence of 1 MAC

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**Statistical Analysis**

Data are expressed as the mean ± SD. Concentration–response curves were determined by fitting the data to the Hill sigmoid pharmacologic model (Origin 5.0; Microcal Software, Northampton, MA) according to the following equation:

$$\text{Aff} = \text{Aff}_0 \cdot (1 + (C_{so} \cdot C^{-1})^n)^{-1}$$

in which Aff is the observed effect at the C concentration, $\text{Aff}_0$ is the maximum effect, $C_{so}$ is the concentra-

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Because desflurane enhanced the positive inotropic effect of dobutamine, we investigated the mechanism of this effect. As previously reported, a group of rats pretreated with reserpine (n = 10). In this group, desflurane abolished the potentiation of the positive inotropic effect of dobutamine (fig. 4).

Because the absence of potentiation of the inotropic effect of dobutamine by most halogenated anesthetic agents contrasts with previous results obtained using a pure β- or pure α-adrenoceptor stimulant, we studied the interaction of isoflurane and dobutamine in the presence of α-adrenoceptor blockade. In the presence of α-adrenoceptor blockade, the positive inotropic effect of dobutamine was slightly greater, but the difference was not statistically significant (AF, Effmax: 208 ± 25% vs. 185 ± 36% of baseline; P = 0.07). Even in the presence of α-adrenoceptor blockade, isoflurane did not potentiate the positive inotropic effect of dobutamine (fig. 5).

### Discussion

Dobutamine exhibited a maximum positive inotropic effect that occurred at 10^{-4} M, as previously reported. The magnitude of this positive inotropic effect of dobutamine was comparable to that of isoproterenol and significantly greater than that of phenylephrine (table 2), and the concentration–response curve of dobutamine was shifted to the right compared with that of isoproterenol, as previously reported. The lusitropic effects of dobutamine differed slightly from those of halothane and desflurane. At 1 MAC, halothane induced a greater decrease in AF (56 ± 18% of baseline) compared with those of isoflurane (90 ± 10%), sevoflurane (92 ± 7%), and desflurane (96 ± 12%). However, because the baseline value of AF differs markedly from one papillary muscle to another, it is difficult to show a pharmacologic effect when using absolute values (fig. 1).

When measured as a percentage of baseline halogenated anesthetic response, the positive inotropic effect of dobutamine was not significantly enhanced in the presence of halothane, isoflurane, and sevoflurane (table 3, fig. 2). We could not accurately study the effects of 2 MAC halothane, because of excessive contractile depression (AF: 37 ± 18% of baseline). In contrast, desflurane significantly potentiated the positive inotropic effect of dobutamine (table 3, fig. 2).

Halothane, isoflurane, sevoflurane, and desflurane did not significantly modify the positive lusitropic effect under low load of dobutamine (fig. 3A). Under high load (R2), the halogenated anesthetics, except halothane, did not significantly modify the lusitropic effects of dobutamine (fig. 3B).

### Table 1. Baseline Values of Mechanical Parameters in the Different Groups of Papillary Muscles

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Vmax (mm/s)</th>
<th>AF (mmN/mm²)</th>
<th>R1</th>
<th>R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>2.08 ± 0.53</td>
<td>22 ± 7</td>
<td>0.72 ± 0.14</td>
<td>1.48 ± 0.19</td>
</tr>
<tr>
<td>Halothane</td>
<td>10</td>
<td>1.88 ± 0.21</td>
<td>19 ± 9</td>
<td>0.75 ± 0.09</td>
<td>1.44 ± 0.15</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>10</td>
<td>2.18 ± 0.01</td>
<td>31 ± 17</td>
<td>0.71 ± 0.12</td>
<td>1.57 ± 0.26</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>6</td>
<td>2.27 ± 0.33</td>
<td>29 ± 15</td>
<td>0.61 ± 0.16</td>
<td>1.53 ± 0.24</td>
</tr>
<tr>
<td>Desflurane</td>
<td>10</td>
<td>2.11 ± 0.46</td>
<td>33 ± 16</td>
<td>0.69 ± 0.20</td>
<td>1.71 ± 0.19</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6</td>
<td>1.69 ± 0.50</td>
<td>20 ± 19</td>
<td>0.84 ± 0.19</td>
<td>1.78 ± 0.09</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

Vmaxₓ = maximum unloaded shortening velocity; AF = isometric active force normalized per cross-sectional area; R1 = [max/Vc/Vmax]; R2 = [dF/dt; dF/dt]

* P < 0.05 versus control group.

### Table 2. Comparison of the Effects of Dobutamine, Isoproterenol, and Phenylephrine on Main Mechanical Parameters of Left Ventricular Papillary Muscle

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vmax (mm/s)</th>
<th>AF (mmN/mm²)</th>
<th>R1 (low load)</th>
<th>R2 (high load)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine (10^{-4} M) n = 10</td>
<td>167 ± 22*</td>
<td>182 ± 32*</td>
<td>79 ± 9*</td>
<td>95 ± 21</td>
</tr>
<tr>
<td>Isoproterenol (10^{-4} M) n = 10</td>
<td>167 ± 20*</td>
<td>166 ± 25*</td>
<td>65 ± 10*</td>
<td>90 ± 9*</td>
</tr>
<tr>
<td>Phenylephrine (10^{-4} M) n = 10</td>
<td>126 ± 10*</td>
<td>137 ± 22*</td>
<td>92 ± 9*</td>
<td>103 ± 8*</td>
</tr>
</tbody>
</table>

Data are mean percent of baseline ± SD.

Vmaxₓ = maximum unloaded shortening velocity; AF = isometric active force normalized per cross-sectional area; R1 = [max/Vc/Vmax]; R2 = [dF/dt; dF/dt]

* P < 0.05 versus control group.

† P < 0.05 versus baseline.
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Table 3. Effects of Halogenated Anesthetics (1 or 2 MAC) on Inotropic and Lusitropic Responses to Dobutamine

<table>
<thead>
<tr>
<th></th>
<th>$V_{\text{max}}$</th>
<th>AF</th>
<th>R1</th>
<th>R2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\text{Eff}_{\text{max}}$ (%)</td>
<td>$C_{50}$ ($\mu$M)</td>
<td>$\text{Eff}_{\text{max}}$ (%)</td>
<td>$C_{50}$ ($\mu$M)</td>
</tr>
<tr>
<td>Control (n = 10)</td>
<td>168 ± 23*</td>
<td>2.3 ± 2.1</td>
<td>185 ± 36*</td>
<td>3.4 ± 2.3</td>
</tr>
<tr>
<td>Halothane 1 MAC (n = 10)</td>
<td>153 ± 33*</td>
<td>5.7 ± 8.3</td>
<td>178 ± 38*</td>
<td>5.6 ± 6.2</td>
</tr>
<tr>
<td>Isoflurane 1 MAC (n = 10)</td>
<td>163 ± 24*</td>
<td>6.4 ± 4.7</td>
<td>172 ± 34*</td>
<td>8.2 ± 6.2</td>
</tr>
<tr>
<td>Isoflurane 2 MAC (n = 6)</td>
<td>168 ± 23*</td>
<td>0.9 ± 0.6</td>
<td>180 ± 23*</td>
<td>2.1 ± 2.1</td>
</tr>
<tr>
<td>Sevoflurane 1 MAC (n = 10)</td>
<td>166 ± 20*</td>
<td>2.7 ± 2.9</td>
<td>190 ± 27*</td>
<td>3.2 ± 5.6</td>
</tr>
<tr>
<td>Sevoflurane 2 MAC (n = 6)</td>
<td>150 ± 19*</td>
<td>6.3 ± 7.4</td>
<td>171 ± 21*</td>
<td>6.7 ± 5.3</td>
</tr>
<tr>
<td>Desflurane 1 MAC (n = 10)</td>
<td>197 ± 22†</td>
<td>2.4 ± 1.4</td>
<td>239 ± 35†</td>
<td>2.1 ± 1.0</td>
</tr>
<tr>
<td>Desflurane 2 MAC (n = 6)</td>
<td>212 ± 32†</td>
<td>7.0 ± 5.2</td>
<td>248 ± 35†</td>
<td>4.7 ± 4.6</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

$V_{\text{max}}$ = maximum unloaded shortening velocity; AF = isometric active force normalized per cross-sectional area; $\text{Eff}_{\text{max}}$ = maximum effect expressed as percent of baseline; $C_{50}$ = concentration that results in 50% of $\text{Eff}_{\text{max}}$; R1 = $\text{max}[\text{V}/V_{\text{max}}]$; R2 = $+dF^{-1} \cdot dt^{-1} - dF^{-1} \cdot dt^{-1}$.

* $P < 0.05$ versus baseline.
† $P < 0.05$ versus control group.

isoproterenol (table 2).2,3 Indeed, whereas $\beta$-adrenergic stimulation induces positive lusitropic effects under low and high load, dobutamine did not exhibit significant lusitropic effects under high load. This result suggests that dobutamine did not modify the calcium myofilament sensitivity. It should be recognized that, despite its wide use in clinical practice, little information is available about the precise effects of dobutamine on intrinsic myocardial contractility10,20,21 and its lusitropic effects.22,23 Indeed, several in vitro studies have shown that dobutamine improved left ventricle relaxation.22,23 But the magnitude of the lusitropic effect of dobutamine is difficult to analyze because of changes in afterload. Furthermore, the fact that relaxation depends on contraction was not accounted for in these in vitro studies. Our results are consistent with the knowledge that dobutamine is an agonist at the $\alpha_1$ and $\beta_1$-myocardial adrenoceptors.21 The differences observed in the effects of dobutamine and isoproterenol (table 2) are also con-

Fig. 1. The effects of 1 minimum alveolar concentration halothane or desflurane on the inotropic effect of dobutamine. Data are absolute mean values of isometric active force (AF) normalized per cross-sectional area ± SD (n = 10 in each group). B1 corresponds to baseline values at a calcium concentration of 0.5 mM. B2 corresponds to baseline values after exposure to halogenated anesthetics in the halothane and desflurane groups. Because the baseline values of isometric active force differ markedly among papillary muscles, it is difficult to show a pharmacologic effect when absolute values are used.

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Fig. 2. The interaction of 1 minimum alveolar concentration halothane or desflurane with increasing concentrations of dobutamine on isometric active force (AF) normalized per cross-sectional area. Data are the mean percentages of baseline ± SD (n = 10 in each group). NS = not significant.
These previous investigations showed that halothane, isoflurane, and sevoflurane potentiated the positive inotropic effects of \( \alpha \)- and \( \beta \)-adrenoceptor stimulations. Furthermore, they emphasized that, although isoflurane and sevoflurane did not modify the positive lusitropic effect of \( \beta \)-adrenoceptor stimulation, \(^3\) halothane alters the positive lusitropic effect of \( \beta \)-adrenoceptor stimulation under low load. \(^2\) These previous studies were performed using isoproterenol or phenylephrine in combination with phenolamine or propranolol, respectively. Therefore, the interaction between the halogenated anesthetics and the adrenoceptor stimulations was assessed only using a pure \( \alpha \)- or \( \beta \)-adrenergic stimulation. In the current experiment, we evaluated the global effect of dobutamine, a clinically useful complex sympathomimetic amine. The inotropic effect of dobutamine, which was initially attributed to stimulation of myocardial \( \beta_1 \) adrenoceptors, \(^26\) is now considered to result from \( \alpha_1 \) and \( \beta_1 \) adrenoceptor stimulation. \(^10,20,21\) Because it has been shown recently that \( \alpha \)-adrenoceptor stimulation may modulate \( \beta \)-adrenoceptor response, \(^11\) we wanted to determine whether such a modulation might explain the lack of enhancement by halogenated anesthetics of dobutamine's inotropic effect. Even after blockade of \( \alpha \) adrenoceptors with phenolamine, isoflurane did not potentiate the inotropic effect of dobutamine (fig. 5). Therefore, we suggest that the absence of interaction

![Graph A](image1)

![Graph B](image2)

**Fig. 3.** The interaction of 1 minimum alveolar concentration halothane or desflurane with increasing concentrations of dobutamine on lusitropy under (A) low (R1) and (B) high (R2) loads. Data are the mean percentages of baseline \( \pm \) SD (\( n = 10 \) in each group). NS = not significant.

consistent with several studies indicating that the cardiac effects of dobutamine differ from those of isoproterenol. Indeed, dobutamine increases heart rate and oxygen consumption less than isoproterenol does. \(^24,25\)

The primary findings of our study focused on the interaction between dobutamine and halogenated agents, which are not consistent with our previous studies of the interaction of halogenated anesthetics with \( \alpha \)- or \( \beta \)-adrenoceptor stimulations in rat myocardium. \(^2,25\)

![Graph C](image3)

**Fig. 4.** The interaction of 1 minimum alveolar concentration desflurane with increasing concentrations of dobutamine on isometric active force (AF) normalized per cross-sectional area in rats that were or were not pretreated with reserpine. Data are the mean percentages of baseline \( \pm \) SD (\( n = 10 \) in each group). NS = not significant.
between halogenated anesthetic agents and dobutamine is related to the characteristics of dobutamine, because its myocardial effects differ from those of isoproterenol and phenylephrine (table 2). Additional studies will be needed to understand, on a molecular basis, the precise reasons for this absence of interaction.

Only desflurane potentiated the positive inotropic effect of dobutamine. To identify the mechanism of this potentiation, we studied rats treated with reserpine, which completely depletes intramyocardial catecholamine stores. After reserpine treatment, desflurane no longer potentiated the positive inotropic effect of dobutamine. Dobutamine may have enhanced the previously described release of catecholamines from intramyocardial sympathetic nerve endings elicited by desflurane. However, by itself, dobutamine has been shown to be devoid of such a presynaptic effect.\(^\text{10}\)

Finally, the halogenated anesthetics, except for halothane, did not modify the lusitropic effects of dobutamine. In the presence of halothane, dobutamine induced a positive lusitropic effect under high load. This result suggests an interaction of halothane and dobutamine at the myofilament level, which unmask some of the effects of dobutamine on myofilament sensitivity. However, the effects of halothane per se on myofilament sensitivity remain controversial.

The following points must be considered when the clinical relevance of our results is assessed. First, this study was conducted at 29°C and at a low-stimulation frequency. Papillary muscles must be studied at this temperature because the mechanical parameters are not sufficiently stable at 37°C and at a low frequency because high-stimulation frequency induces core hypoxia. Second, the study was performed using the rat myocardium, which differs from human myocardium. The density of α adrenoceptors and, consequently, the positive inotropic effect induced by their stimulation are greater in rats than in humans. Nevertheless, the relative importance of α adrenoceptors in cardiac contractility can be increased in disease conditions.

In isolated rat myocardium, halogenated anesthetics did not modify the inotropic effects of dobutamine. Only desflurane enhanced the positive inotropic effect of dobutamine, but this effect was related to the desflurane-induced release in intramyocardial catecholamine stores.

References


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