Superiority of Desflurane over Sevoflurane and Isoflurane in the Presence of Pressure-overload Right Ventricle Hypertrophy in Rats

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ABSTRACT

Background: Pulmonary hypertension and associated pressure-overload right ventricular (RV) hypertrophy represent a tremendous challenge for the anesthesiologist, as optimal perioperative management is mandatory. However, the ideal anesthetic agent remains unknown because scientific evidence is lacking.

Methods: Twenty-eight rats were randomly assigned to a control or a monocrotaline group (60 mg kg\(^{-2}\)). Four weeks later, animals were anesthetized, instrumented with a RV conductance catheter, and underwent well-controlled dose-responses to isoflurane, desflurane, and sevoflurane inhalation (minimum alveolar concentrations 0.5, 1.0, 1.5).

Results: Compared with controls, rats injected with monocrotaline presented with RV hypertrophy, increased afterload, and contractility, without change in cardiac output. The ratio of pressures in the right over the left circulation increased. The halogenated volatiles differently altered hemodynamics. Sevoflurane reduced RV contractility (more than 50%) and the right over left pressures ratio increased (from 0.41 ± 0.08 [SD] to 0.82 ± 0.14; \(P < 0.0001\)) to profound concomitant systemic vasodilation, demonstrating a critical pressure gradient between right and left circulations. Despite significantly higher RV systolic pressures and afterload, desflurane decreased RV contractility much less (<10%; \(P < 0.0001\) vs. sevoflurane) and maintained the right over left pressures ratio at more favorable values (0.47 ± 0.07; \(P < 0.0001\) vs. sevoflurane). Isoflurane presented intermediate effects.

Conclusion: In the presence of pressure-overload RV hypertrophy, hemodynamics are better preserved under desflurane inhalation, whereas sevoflurane—and to a lesser extent isoflurane—cause large discrepancies in the left and right circulations, raising the ratio of the pulmonary to systemic circulations to critical levels.

What We Already Know about This Topic

- Intraoperative management of pulmonary hypertension remains a tremendous clinical challenge
- This study evaluated and compared the hemodynamic repercussions of three frequently used volatile agents (isoflurane, desflurane, and sevoflurane) in the presence of pressure-overload right ventricular hypertrophy in a in situ rat heart model

What This Article Tells Us That Is New

- Desflurane produced minimal systemic and right ventricular effects most probably related to its ability to relatively preserve sympathetic tone, whereas sevoflurane—and to a lesser extent, isoflurane—caused large discrepancies in the left and right circulations, characterized by marked reduction in left ventricular afterload combined with reduced right ventricular inotropy raising the ratio of the pulmonary to systemic circulations to critical levels

Under the denomination of pulmonary hypertension (PH) are grouped five entities (pulmonary arterial hypertension; PH with left heart disease; PH associated with lung diseases and/or hypoxemia; PH due to chronic thrombotic and/or embolic disease; miscellaneous [revised World Health Organization classification])\(^1\) that all share in common hemodynamic modifications of the pulmonary vasculature leading to a chronically increased intravascular pressure, defined as a mean pulmonary arterial pressure above 25 mmHg at rest,\(^2\) and resulting in eventual right ventricular (RV) failure.

The prevalence of PH in the population is dependent on its etiology. In a French registry, the prevalence of pulmonary arterial hypertension was approximately 15 per million.\(^5\)
Moreover, the number of patients with PH related to chronic left heart disease or chronic hypoxic states is far greater.\textsuperscript{4} An estimated prevalence of PH in patients with obstructive sleep apnea was approximately 15--20%.\textsuperscript{5} It is therefore not infrequent that anesthesiologists are confronted with such patients.

However, intraoperative management of PH is a tremendous challenge. Indeed, surgery is a period at significant risk for patients with PH. In a series of PH patients undergoing noncardiac surgery, the mortality rate was found to be 7%.\textsuperscript{6} The risk of developing a postoperative morbid event was up to 42%, with respiratory failure, cardiac dysrhythmia, and congestive heart failure being the leading causes. Another retrospective study reported that PH patients undergoing total hip or knee arthroplasty experienced an approximately 4- to 4.5-fold increased adjusted risk of mortality.\textsuperscript{7}

It is therefore mandatory to take care of these patients with great concern during the perioperative period. The main goals are to maintain adequate preload, systemic vascular resistance (SVR), and ventricle contractility, as well as to prevent increases in pulmonary vascular resistance.\textsuperscript{8} In this view, the choice of the anesthetic agent should be highly regarded. Unfortunately, although it is known that nitrous oxide should be avoided because of concern of elevation in pulmonary vascular resistance with this gas, there are no clinical trials assessing the different volatile anesthetics. Furthermore, despite published animal studies on the effects of halogenated volatiles on the right ventricle and/or pulmonary circulation, the question of whether an anesthetic agent is more appropriately suited for PH patients is still unanswered.

We thus designed an experimental study to evaluate and compare the hemodynamic repercussions of three frequently used volatile agents (isoflurane, desflurane, and sevoflurane) in the presence of pressure-overload RV hypertrophy in a model of \textit{in situ} heart preparation in rats. We elected to use the well-described rodent model of chronic PH injecting a single subcutaneous dose of monocrotaline, a toxic pyrrolizidine alkaloid found in the plant \textit{Crotalaria spectabilis}, that causes acute and subacute damages of the peripheral vasculature of the lung through early adventitial inflammation followed by progressive smooth muscle hypertrophy in the media.\textsuperscript{9}

**Materials and Methods**

**Animals**

Approval from the Ethics Committee for Animal Research of the University Medical Center and from the Cantonal Veterinary Office of Geneva, Switzerland, was achieved before the study was initiated. Handling of animals followed the guidelines laid out in the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, 1996).

Twenty-eight male adult Wistar rats (mean weight, 393 ± 57 g) were used for this study. Each rat was randomly assigned either to the control (n = 14) or to the monocrotaline group (n = 14). All rats were maintained in temperature- and humidity-controlled rooms with typical light-dark cycle and given standard chow and tap water \textit{ad libitum} until the operating day. A single subcutaneous injection of monocrotaline (Crotaline C2401, Sigma–Aldrich, Buchs, Switzerland), 60 mg kg\textsuperscript{-1}, was performed on day 1 in the monocrotaline group and the rats were observed and kept in the laboratory (including rats of the control group) during 28 days before instrumentation.

**Surgical Preparation**

The rodents were anesthetized by halogenated volatile inhalation and intubated by direct laryngoscopy with a 14-gauge catheter (100% oxygen during induction until intubation). Spontaneous ventilation was maintained as long as the sternotomy was not performed to avoid acute positive pressure-induced circulatory decompensation, as was observed in a pilot study we conducted before these experiments. The halogenated volatile (isoflurane [Baxter, Volketswil, Switzerland], desflurane [Baxter, Volketswil, Switzerland] or sevoflurane [Abbott, Baar, Switzerland]) used for induction was randomly chosen and the anesthesia was maintained with the same volatile throughout the surgical preparation adjusted at a concentration allowing unreactive surgery (approximately 1.0–1.5 minimum alveolar concentration [MAC]). The left femoral artery and the left femoral vein were catheterized with 22-gauge catheters advanced into the inferior aorta and vena cava, respectively. Intravascular volume status was maintained by an infusion of sodium chloride 0.9%, 0.4 ml h\textsuperscript{-1}. Before opening the chest, 10 mcg kg\textsuperscript{-1} fentanyl (Sintetica, Mendrisio, Switzerland) were bolused before starting an infusion of 10 mcg kg\textsuperscript{-1} h\textsuperscript{-1} fentanyl. A bolus of 1 mcg kg\textsuperscript{-1} atracurium (GlaxoSmithKline, Münchenbuchsee, Switzerland) was also administered for muscular relaxation. Then, the sternotomy was performed to enter the chest and the rats were ventilated (40% O\textsubscript{2} in air) with a constant volume-cycled rodent ventilator (tidal volume, 7 ml kg\textsuperscript{-1}; positive end-expiratory pressure, 2.5 cm H\textsubscript{2}O; respiratory rate, 70–80 min\textsuperscript{-1}). A 3-0 polypropylene suture was placed around the inferior vena cava (IVC) for intermittent vascular occlusion analysis. Finally, an apical stab with a 30-gauge needle was made in the right ventricle before it was catheterized with a 1.9 F conductance pressure-volume (PV) catheter (Scisense Inc, London, Ontario, Canada). The catheter was advanced along the long axis of the ventricle. The correct position was determined by phase and magnitude signals, as well as by online visualization of the PV loops and ability to modify the PV loops when altering preload through IVC occlusion. After surgical preparation, an arterial blood sample was collected for hematocrit and blood gas analysis to check for gas exchange. The entire instrumentation process lasted approximately 60 min.
Airway pressure and respiratory gases (including precise expiratory concentration of halogenated volatiles) were continuously monitored (Ultima™, Datex/Instrumentarium, Helsinki, Finland). Due to the small size of the rats compared with the relatively large gas sampling rate of the Datex monitor, expired gases were not directly sampled at the usual level of the intratracheal catheter but from a sidestream port connected to the expiratory tubing leading to the waste anesthetic gases scavenging system, 10 cm downstream the water-filled positive end-expiratory pressure device of the rodent ventilator. This allowed continuous and stable recording of expiratory gases concentration that are dumped over the expiratory duration (i.e., not true end-expiration) resulting in measured carbon dioxide values of approximately 2.8–3.2% during normoventilation. The rats were placed on a homeothermic blanket system (Harvard Apparatus, Holliston, MA) to maintain body temperature at 37°C.

Assessment of Cardiovascular Function

The conductance catheter placed in the right ventricle was connected to the recently developed ADVantage™ system (Scisense Inc). This system uses a continuous dynamic correction for parallel conductance and can be repeatedly calibrated in vivo without the need for hypertonic saline. It was shown to accurately measure beat-by-beat pressure and volume in the mouse right ventricle. It allowed the continuous recording of ventricular pressure and volume, steady-state and dynamic PV loops during the temporarily occlusion of the vena cava, and the classic ventricular function parameters derived from these recordings. In addition, catheters introduced in the femoral artery and vein were connected to calibrated pressure transducers (Honeywell, Zürich, Switzerland), and allowing the recording of systemic arterial and venous pressures.

Experimental Protocol

Each rat was exposed to stepwise increasing doses (MAC 0.5, 1.0, and 1.5) of isoflurane, desflurane, and sevoflurane. MAC 1.0 for isoflurane was 1.5%, MAC 1.0 for desflurane was 5.7%, and MAC 1.0 for sevoflurane was 2.7%. The sequence of anesthetics was determined by random chance.

Data Acquisition and Treatment

The various recorded variables were continuously recorded and stored at a sampling rate of 1,000 Hz via an analog/digital interface converter (Biopac System, Goleta, CA) on a personal computer. Data were then analyzed using waveform data acquisition/analysis software (AcqKnowledge, Biopac System) and further analyzed with Microsoft Excel.

Data were obtained first at MAC 0.5 and then under stepwise increase of gas concentrations. Hemodynamic measurements were collected at each anesthetic concentration of the same volatile after 5 min of equilibration. When the rats were exposed to another volatile, the measurements were collected after 20 min of equilibration. For each condition, analyzed data were obtained after a 5-s period of apnea at end-expiration (five stable cardiac cycles that were averaged), followed by gradual preload reduction through manual IVC occlusion, still during apnea. IVC occlusion generally yielded 10–20 cardiac cycles allowing off-line reconstruction of PV loops and their derived parameters.

The procedure for the PV loops analysis, adapted here for the right ventricle, was already described elsewhere. Briefly, PV loops were plotted during the IVC occlusion to define the end-systolic pressure-volume relationship (ESPVR), its linear slope measured in the operating range (Esv, end-systolic elastance) and its volume-axis intercept (Vs), through logarithmic extrapolation of the ESPVR. Preload recruitable stroke work (PRSW), which is the slope of the stroke work–end-diastolic volume relationship, was also determined.

From steady-state PV recordings, we derived the following parameters: heart rate, RV end-diastolic pressure (EDP), RV end-systolic pressure (ESP), RV end-diastolic volume (EDV), RV end-systolic volume, RV stroke volume (SV = EDV – end-systolic volume), RV cardiac output (CO = Heart Rate x SV), RV ejection fraction (EF = SV/EDV), the peak positive value of the time-derivative of RV pressure (dP/dt max), the peak negative value of the time-derivative of RV pressure (dP/dt min), RV preload-adjusted dP/dt max (PAdP/dt max = dP/ d max /EDV), RV stroke work (SW = SV x [ESP-EDP]), the pulmonary arterial effective elastance (Ea = ESP/SV), the RV ventriculoarterial coupling efficiency (Ea/Ea), and the time relaxation constant τ, being defined as the time span between the time of dP/dt min in the cycle to the point where the RV pressure signal drops below the EDP level.

From the arterial pulse pressure recordings, we derived: systolic and diastolic systemic arterial pressure, mean systemic arterial arterial pressure (MAP), systemic pulse pressure and SVR (SVR = [MAP - inferior vena cava pressure]/CO), assuming that the left ventricular CO equals the RV CO. Finally, we computed the ratio of peak systolic RV pressure over peak systemic arterial pressure (right/left systolic vascular ratio, R/L) to characterize the beat to beat relationship between the right and left circulations.

Each of these steady-state parameters was averaged from five consecutive heart cycles during the stable apnea condition immediately preceding the IVC occlusion maneuver.

Morphometric Data

After sacrifice of the animals with potassium chloride under maximal volatile inhalation, the heart was dissected with the atria removed and frozen for morphometric analysis. The hearts were then cut to transverse slices of 2 mm and scanned. The midventricular slice was used to estimate the ratio of RV over left ventricular wall thickness ratio (using three lines with different directions passing through the center of the heart). The weight of the left ventricle (+ septum) and right ventricle were determined by reassembling the respective
Anesthesiology 2012; 117:1051–61

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wall slices. A technical assistant, blinded to the rat's group, handled the morphometric analysis.

Statistical Analysis
Analyses were performed with GraphPad Prism®, version 5.04 (GraphPad Software, Inc., La Jolla, CA). Data are reported as means ± SD. Morphometric and blood gas analysis data between control and monocrotaline groups were compared using a Student unpaired t test. The effects of monocrotaline at the three drug concentrations were characterized by a two-way repeated measures ANOVA with drugs and treatments as factors, followed by Bonferroni posttests for multiple comparisons when P < 0.05. Furthermore, comparisons within the three volatiles in each treatment group were analyzed by a one-way repeated measures ANOVA, with Bonferroni correction. Relationships between selected variables were evaluated by linear correlation using Pearson correlation coefficient.

Results
Twenty-eight rats were randomized. Of the 14 rats in the control group, we analyzed data from 12 rats; two rats were excluded because their baseline RV ESP was above 30 mmHg. In the monocrotaline group, one rat was found dead on the day of the experiment and two other rats died from acute hemodynamic decompensation during the surgical preparation. Therefore, we analyzed data from 11 rats.

Effects of Monocrotaline Injection
Morphometric data are reported in table 1 and macroscopic changes secondary to monocrotaline injection are shown in figure 1. Mean heart weight and mean left ventricle weight were not different between the two groups, whereas mean right ventricle weight was statistically different between the control and the monocrotaline group (127 ± 31 mg vs. 163 ± 40 mg, respectively; P = 0.025), as was the ratio of the right over left ventricle wall thickness (29.9 ± 7.0% vs. 41.8 ± 5.7%, respectively; P < 0.0001).

Table 1. Morphometric Data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Monocrotaline</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart weight, mg</td>
<td>973 ± 150</td>
<td>1,032 ± 165</td>
<td>0.383</td>
</tr>
<tr>
<td>Left ventricle weight, mg</td>
<td>846 ± 132</td>
<td>869 ± 147</td>
<td>0.705</td>
</tr>
<tr>
<td>Right ventricle weight, mg</td>
<td>127 ± 31</td>
<td>163 ± 40</td>
<td>0.025</td>
</tr>
<tr>
<td>Right/left ventricle wall thickness, %</td>
<td>29.9 ± 7.0</td>
<td>41.8 ± 5.7</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. Control group, n = 12; monocrotaline group, n = 11. P values from Student unpaired t test.

Table 2. Blood Gases at the Beginning and the End of the Study (FiO₂ = 0.4)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Monocrotaline</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.47 ± 0.04</td>
<td>7.44 ± 0.04</td>
<td>0.0548</td>
</tr>
<tr>
<td>Final</td>
<td>7.49 ± 0.07</td>
<td>7.44 ± 0.03</td>
<td>0.0537</td>
</tr>
<tr>
<td>Paco₂, mmHg</td>
<td>Baseline</td>
<td>33.8 ± 3.7</td>
<td>0.9893</td>
</tr>
<tr>
<td>Final</td>
<td>28.5 ± 5.3*</td>
<td>30.0 ± 5.6</td>
<td>0.5247</td>
</tr>
<tr>
<td>Pao₂, mmHg</td>
<td>Baseline</td>
<td>188 ± 28</td>
<td>0.0587</td>
</tr>
<tr>
<td>Final</td>
<td>202 ± 13</td>
<td>169 ± 43</td>
<td>0.0296</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. Control group, n = 12; monocrotaline group, n = 11. P values from Student unpaired t test. *P < 0.05 compared with baseline value from Student paired t test.

Fig. 1. Representative midinterventricular septum transverse sections of hearts from a control (A) and a monocrotaline-treated rat (B). Scale bar in millimeters.

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### Table 3. Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Monocrotaline (MCT)</th>
<th>Drug Effect</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bpm</td>
<td>399.47</td>
<td>398.37</td>
<td>-1.0</td>
<td>0.394</td>
</tr>
<tr>
<td>MAP</td>
<td>110.02</td>
<td>119.18</td>
<td>64.14***</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PP</td>
<td>0.55</td>
<td>0.54</td>
<td>0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>mmHg</td>
<td>16.47</td>
<td>18.10</td>
<td>6.03</td>
<td>0.0001</td>
</tr>
<tr>
<td>SVR</td>
<td>1.5</td>
<td>1.8</td>
<td>0.29</td>
<td>0.19</td>
</tr>
<tr>
<td>mmHg/mL</td>
<td>0.3</td>
<td>0.2</td>
<td>0.01</td>
<td>0.053</td>
</tr>
<tr>
<td>CO</td>
<td>49.47</td>
<td>51.68</td>
<td>2.21</td>
<td>0.109</td>
</tr>
<tr>
<td>ml/min</td>
<td>39.89</td>
<td>43.39</td>
<td>3.50</td>
<td>0.0098</td>
</tr>
<tr>
<td>EF</td>
<td>33.82</td>
<td>38.15</td>
<td>4.33</td>
<td>0.0008</td>
</tr>
<tr>
<td>%</td>
<td>29.07</td>
<td>28.73</td>
<td>0.34</td>
<td>0.609</td>
</tr>
<tr>
<td>ES</td>
<td>0.24</td>
<td>0.21</td>
<td>0.02</td>
<td>0.597</td>
</tr>
<tr>
<td>mmHg/g</td>
<td>0.20</td>
<td>0.19</td>
<td>0.01</td>
<td>0.949</td>
</tr>
<tr>
<td>Ees</td>
<td>0.27</td>
<td>0.26</td>
<td>0.01</td>
<td>0.597</td>
</tr>
<tr>
<td>mmHg/g</td>
<td>0.23</td>
<td>0.24</td>
<td>0.02</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ees/Ees</td>
<td>0.15</td>
<td>0.12</td>
<td>0.37</td>
<td>0.001</td>
</tr>
<tr>
<td>dp/dtmax</td>
<td>143.62</td>
<td>141.51</td>
<td>2.10</td>
<td>0.0001</td>
</tr>
<tr>
<td>mmHg/1</td>
<td>15.79</td>
<td>15.68</td>
<td>0.11</td>
<td>0.925</td>
</tr>
<tr>
<td>SV</td>
<td>3.41</td>
<td>4.20</td>
<td>0.03</td>
<td>0.0001</td>
</tr>
<tr>
<td>SW</td>
<td>3.10</td>
<td>3.07</td>
<td>0.02</td>
<td>0.027</td>
</tr>
<tr>
<td>ml/g</td>
<td>2.68</td>
<td>2.68</td>
<td>0.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>PRSW</td>
<td>17.27</td>
<td>17.33</td>
<td>0.77</td>
<td>0.0001</td>
</tr>
<tr>
<td>ml/g</td>
<td>15.2</td>
<td>15.46</td>
<td>2.77</td>
<td>0.0001</td>
</tr>
<tr>
<td>dp/dtmin</td>
<td>1.19</td>
<td>1.20</td>
<td>0.67</td>
<td>0.0001</td>
</tr>
<tr>
<td>ml/g/1</td>
<td>1.34</td>
<td>1.34</td>
<td>0.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>mE/Ees</td>
<td>9.22</td>
<td>9.22</td>
<td>0.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>10.1</td>
<td>9.71</td>
<td>12.05</td>
<td>0.17</td>
<td>0.0001</td>
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</tbody>
</table>

Values are expressed as means ± SD. Control group, n = 12; monocrotaline group, n = 11. P values from two-way repeated measures ANOVA with treatment (“MCT effect”) and drugs (“Drug effect”) as factors. *P < 0.05, **P < 0.01, ***P < 0.001 vs. dose-matched isoflurane of corresponding treatment from Bonferroni posttests for multiple comparisons.

CO = RV cardiac output; dp/dt\text{max} = peak positive value of the time-derivative of RV pressure; dp/dt\text{min} = peak negative value of the time-derivative of RV pressure (data are expressed as x’); E\text{es} = pulmonary arterial effective elastance; E\text{es}/E\text{es} = ratio of E\text{es} over E\text{es} right ventriculoarterial coupling efficiency; E\text{dp}/dp\text{dp} = RV end-diastolic pressure; E\text{dp}/dp\text{dp} = RV end-diastolic volume; E\text{dp} = RV ejection fraction; ESP = RV end-systolic pressure; HR = heart rate; MAC = minimum alveolar concentration; MAP = mean systemic arterial pressure; PaP/dt\text{max} = preload-adjusted dp/dt\text{max}; PP = systemic pulse pressure; PRSW = RV preload recruitable stroke work; R/L = ratio of peak systolic RV pressure over peak systemic arterial pressure; SV = RV stroke volume; S\text{VR} = systemic vascular resistance; SW = RV stroke work; V\text{e} = volume axis intercept of the RV ESPVR (logarithmic extrapolation); T = RV relaxation time constant.
Effects of Isoflurane

In the control group, increasing isoflurane concentration to MAC 1.5 produced its expected systemic vascular effects, i.e., a 40% decrease in SVR (P < 0.0001) associated with profound hypotension (P < 0.0001) and a moderately reduced heart rate (P < 0.05; table 3). At MAC 1.0, isoflurane had no significant effect on these systemic variables, except for an intermediately reduced MAP (P < 0.001). Systemic vasodilation was accompanied by an increased venous return to the RV (15% rise in EDV at MAC 1.5, P < 0.01) without changes in RV ESP and EDP nor SV or CO. However, because of the major effect on the systemic circulation, the R/L ratio was significantly increased at MAC 1.0 and MAC 1.5 (P < 0.05 and P < 0.0001, respectively). RV contractility, as measured by dP/dt max, was significantly decreased at MAC 1.5 (P < 0.01 and P < 0.001, respectively), whereas SW and PRSW remained unchanged. The slope of the RV ESPVR, E a, and its volume-axis intercept, V 0, were significantly affected by isoflurane at MAC 1.5, with a flattening and rightward shift of the ESPVR. E a did not change but the E a/E o ratio was significantly decreased (P < 0.05). Isoflurane also caused slight diastolic dysfunction, as demonstrated by an increased τ at MAC 1.5 (P < 0.05), but no change in dP/dt min.

In the monocrotaline group, isoflurane produced similar dose-dependent effects as those seen in the control group (table 3). Because of the monocrotaline-induced increased RV afterload and contractility during MAC 0.5 inhalation, increasing the concentration of isoflurane to MAC 1.5 induced in addition significant reduction in ESP, SW, PRSW, and dP/dt min, that had not been observed in the control group. Despite these RV depressant effects secondary to isoflurane inhalation, values of ESP, E o, SW, PRSW, and dP/dt min as well as dP/dt max, PAdP/dt max, and R/L remained significantly higher in the monocrotaline group compared with the control group during MAC 1.5 isoflurane inhalation.

Effects of Desflurane

In the control group, desflurane at MAC 1.5 reduced heart rate (P < 0.01) and MAP (P < 0.0001), but had no significant effect on systemic pulse pressure or SVR (table 3). ESP (P < 0.001), EDP (P < 0.05), EDV (P < 0.05), and the R/L ratio (P < 0.0001) were all slightly though significantly increased. SV (P < 0.05), CO (P < 0.0001), and EF (P < 0.001) decreased. Desflurane did not modify dP/dt max, SW, nor PRSW, but the PAdP/dt max was slightly
Effects of Sevoflurane

In the control group, sevoflurane produced major dose-dependent decreases of systemic hemodynamics, i.e., SVR, MAP, systemic pulse pressure, and heart rate (P < 0.0001 for all variables). RV ESP was also slightly though significantly reduced (P < 0.0001), and the R/L ratio increased more than twofold (P < 0.0001). Contractility indices dP/dt max, PAdP/dt max, SW, and PRSW were also intensely decreased (35–40% at MAC 1.5; P < 0.0001). The combined systemic vascular and cardiac effects resulted in a reduced ejection capacity with diminished SV, EF, and CO (P < 0.0001), associated with an increased EDV (P < 0.0001). Sevoflurane did not modify Er, Ees, and Ees/Ees, but Ver increased (P < 0.0001). Finally, sevoflurane also reduced diastolic function, as shown by the decrease in dP/dt min (P < 0.0001) and the increased τ (P < 0.0001).

In the monocrotaline group, sevoflurane produced similar dose-dependent effects as those seen in the control group (table 3), except for PRSW, which was not statistically decreased because of a large individual variability with this index. As was observed with isoflurane and desflurane, afterload and contractility indices remained significantly higher in the monocrotaline group compared with the control group during MAC 1.5 desflurane inhalation.

Differences between the Halogenated Volatiles

In the control group, baseline hemodynamic values (i.e., MAC 0.5) were similar for the three volatiles (table 3). However, the investigated volatile agents produced major and significantly different variations in systemic and RV hemodynamics following stepwise increases in MAC. On the systemic circulation, sevoflurane produced the most profound drop in MAP, systemic pulse pressure, and SVR, followed by isoflurane, then by desflurane. Sevoflurane was also associated with the most important alterations of RV systolic and diastolic functions, again followed by isoflurane, then by desflurane. On the other hand, desflurane was the only drug to increase ESP and EDP, associated with a significant increase in Ees.

As was the case with the control group, systolic and diastolic functions in the monocrotaline group were more affected by sevoflurane. It should be noted that despite the fact that ESP and Ees were higher with desflurane and that pulmonary vascular resistance seemed enhanced as suggested by the relatively steeper relationship between ESP and CO compared with isoflurane and sevoflurane in figure 3, there was not associated with a reduced contractility, dP/dt max and PAdP/dt max or SW and PRSW showing little or no variations of their values with increasing desflurane concentrations.

Discussion

Model of Compensated, Pressure-overload RV Hypertrophy

After monocrotaline injection, right ventricle weight and wall thickness were increased (fig. 1, table 1) and Pao2 levels were lower (table 2), the latter being most probably secondary to moderate ventilation/perfusion mismatches. ESP and Ees were increased, demonstrating indirectly that pulmonary arterial pressure was genuinely increased. The right ventricle adapted through concentric hypertrophy, further evidenced by changes in diastolic function.

Ees was steeper in the monocrotaline group, suggesting increased contractility, but as already reported both for the left ventricle,15 and the right ventricle,16 this could be only secondary to the increased afterload. V0, on the other hand, was not significantly increased. PRSW was previously demonstrated to be the most reliable index of RV contractile performance.16 However, our results show that PRSW cannot be applied to pressure-overload RV hypertrophy. Whereas the correlation coefficient of the relationship between dP/dt max and PRSW was quite satisfactory in the control group (R² = 0.646), it was very poor in the monocrotaline group (fig. 5). This can partly be explained by a large individual variation for PRSW in the monocrotaline group, which was not the case with the simultaneously recorded dP/dt max values. Because of concerns about the validity of indices derived from PV loop analysis in hypertrophied RV, dP/dt max and PAdP/dt max were considered throughout this study as reference contractile indices (note the high correlation coefficient between dP/dt max and PAdP/dt max in both groups [fig. 5]). One can argue that dP/dt max is afterload dependent and was then increased in the monocrotaline group only because of enhanced afterload. However, CO and EF were identical in both groups, despite higher SW in the monocrotaline group. This could not have been the case without an effective enhanced contractility.
slight reduction in MAP with no significant changes in SVR, probably secondary to systemic toxic effects.21

Effects of the Halogenated Volatiles

All three halogenated volatiles produced consistent systemic hemodynamic variations, but the magnitude of these variations were clearly dependent on the volatiles used. Although desflurane decreased MAP by approximately 20–25% at MAC 1.5, MAP was decreased by 60–65% with sevoflurane; isoflurane produced intermediate effects. Moreover, desflurane did not significantly affect SVR, whereas sevoflurane induced profound vasodilation. Surprisingly, these disparities of the three investigated agents on SVR have not previously been specifically reported.19,22,23 This discrepancy may be related to species differences, differing baseline systemic vascular tone, disparate applied drug concentrations, but most probably also to the experimental protocol used. For instance, in a rabbit study,25 the concentrations of the inhalation agents were adjusted to the individual animal’s response to deep paw pinch compared with the strictly imposed MAC of the current study, resulting in differing baseline and final MAC between studies. Rabbits were further hyperventilated to avoid spontaneous breathing during recordings while we supplemented general anesthesia with a continuous infusion of fentanyl and atracurium to prevent this occurrence. These differences may have influenced the underlying sympathetic tone between the studies, a consequence that is especially relevant for the cardiovascular effects of desflurane.24

On the right circulation, there was no major vasodilation of the pulmonary vasculature in the control group, even with the potent systemic vasodilating sevoflurane, as assessed by E\textsubscript{a}, or indirectly by ESP. This is in agreement with previous studies demonstrating that isoflurane, desflurane, and sevoflurane do not affect the pulmonary arterial pressure-flow relationship, i.e., vascular tone.25–27 During conditions of an increased RV afterload, ESP was reduced with isoflurane and sevoflurane, but this decrease was clearly flow-related (fig. 3), indicating that these agents did not actively vasodilate the pulmonary vasculature during the relatively fixed monocrotaline-induced PH.

It should be observed that the common cardiac functional indices used in clinical practice, i.e., CO and EF, are not sensitive enough to distinguish between halogenated volatiles in the presence of pressure-overload RV hypertrophy. This is also true for the indices derived from the PV loops. Indeed, whereas the hemodynamics were profoundly disturbed by sevoflurane and isoflurane, neither E\textsubscript{a} nor the E\textsubscript{a}/E\textsubscript{e} ratio showed consistent changes in myocardial contractility and coupling efficiency and therefore did not add substantial information in this respect. The large variability of the PRSW index also precluded its use in this situation. The aptitude to detect dysfunction of the right ventricle with PV loop-derived contractility indices was therefore limited; in any case, V\textsubscript{e} seemed a more reliable index. In contrast, Pd.dp/dt\textsubscript{max} was much more consistent with observed and coherent contractility
changes. This index has previously been shown to be preload and afterload independent, at least for the left ventricle.15

The current study shows that isoflurane, desflurane, and sevoflurane exhibit different effects on the RV systolic and diastolic function in the presence of pressure-overload RV hypertrophy. Of interest, we have shown that desflurane is the best choice, sevoflurane the worst. RV contractility was indeed better preserved with desflurane. However, a better RV contractility does not by itself explain why rats were more stable under desflurane exposure, because, at all times and under all volatiles, dP/dtmax and PAdP/dtmax remained higher in the monocrotaline versus control group. More importantly, systemic hemodynamics, especially LV afterload, were less altered by desflurane. The right-to-left gradient of vascular pressures is conserved under desflurane and prevents the left ventricle from being crushed by the right ventricle through septal ballooning, leading to reduced LV compliance and filling. This point is best demonstrated by analysis of the R/L ratio, which was less increased with desflurane than with the two other volatiles (fig. 4). It should be observed that with sevoflurane, R/L was close to 1, meaning that pressures in the pulmonary circulation almost equaled pressures in the systemic circulation. The relationship between PAdP/dtmax and R/L shows that a reduction in RV contractility is directly associated with a concomitant increase in R/L (fig. 6). After monocrotaline injection, the x-axis intercept of this relationship is displaced to the right while the slope remains identical. This means that for any given PAdP/dtmax value, R/L will be closer to 1 in the presence of a pressure-overload RV hypertrophy. One can understand that the slightest decrease in left ventricle myocardial contractility becomes harmful. Moreover, if left ventricle afterload is suddenly decreased, acute heart failure can happen even at high levels of RV contractility. This implies that it is safer to keep systemic hemodynamics in physiologic ranges, rather than trying to decrease the pulmonary vascular pressures by choosing a specific halogenated volatile more prone to induce pulmonary vasodilation, at the cost of also altering systemic pressures. Indeed, if we had based our interpretation only on the right circulation regardless of the left, sevoflurane would have seemed the ideal drug because RV afterload was apparently reduced. However, based on R/L, it would be strongly recommended not to use sevoflurane in this setting, but rather to choose desflurane to avoid an acute

Fig. 5. Relationship between right ventricle dP/dtmax and PRSW (A) or PAdP/dtmax (B) of the three different concentrations of each inhalation agent. Lines represent linear correlations with their coefficients of determination of pooled means during control (triangles, solid line) and following monocrotaline pretreatment (circles, dashed line). Symbols are the same as in figure 3. Note the very large variability and poor relationship with the PRSW index in monocrotaline treated animals. PAdP/dtmax = preload-adjusted dP/dtmax; PRSW = preload recruitable stroke work.

Fig. 6. Relationship between mean values of right ventricle preload-adjusted dP/dtmax (PAdP/dtmax) and the right/left systolic vascular ratio (R/L) of the three different concentrations of each inhalation agent illustrating the combined effect of monocrotaline and the anesthetic drugs. Lines represent linear correlations of pooled means during control (triangles, solid line) and following monocrotaline pretreatment (circles, dashed line). Symbols are the same as in figure 3.

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left ventricle failure secondary to reduced filling of the rats’ left ventricle.

**Study Limitations**
We studied an animal model of PH and pressure-overload RV hypertrophy secondary to monocrotaline injection, a condition known to be curable by many different pharmacologic agents. The pathophysiologic model is therefore not necessarily identical to what can be observed in established clinical PH. Nonetheless, monocrotaline’s repercussion on the right ventricle, i.e., pressure-overload hypertrophy, is not different from any chronic compensatory ventricle change associated with increased afterload observed in sustained PH.

Hemodynamic data related to the left ventricle are lacking. Clearly, left contractility indices would have been valuable to better understand how the hypertrophied right ventricle affects the left ventricle. It was yet technically difficult to introduce a second catheter in the left ventricle and harmful to already sick, potentially unstable rats. Artifacts caused by the presence of two catheters in the heart also prevented reproducible measures of good quality. We decided to record systemic variations through a femoral catheter advanced into the aorta and to assume that CO was identical in the left and in the right ventricles. It was also for technical reasons that we did not measure pressures or resistances in the pulmonary vasculature.

The current study was conducted in open-chest animals, abolishing chest wall-heart interaction. In a closed chest, the described effects on the R/L ratio would have been amplified and its potentially harmful consequences even more readily obtained. This last point is further supported by the observation that the two rats injected with monocrotaline that died during the surgical preparation were anesthetized with sevoflurane, the agent associated with the highest R/L ratio.

Finally, the statistical analysis used a two-way repeated measures ANOVA that was followed by Bonferroni posttests when P < 0.05. We understand that multiplicity is problematic as repeating the procedure for the three dosages is not adjusted. However, many comparisons were needed to illustrate the behavior of each drug. The interpretation of the individual main effects is also made easier (each effect has its own exact P value).

**Conclusion**

The current results demonstrate that in rats the cardiovascular properties of the halogenated volatiles commonly used in clinical practice are not equal and that their use may present substantial hemodynamic risks in the setting of pressure-overload RV hypertrophy. Desflurane produced minimal systemic and RV effects most probably related to its ability to relatively preserve sympathetic tone, whereas sevoflurane—and to a lesser extent isoflurane—cause large discrepancies on the left and right circulations, characterized by marked reduction in LV afterload combined with reduced RV inotropy, increasing the ratio of the pulmonary to systemic circulations to critical levels. The R/L ratio should be taken into account when evaluating inhalation anesthetics because the classic PV loop derived as well as clinical performance indices are not sufficiently sensitive to detect these critically risky conditions. Because of the probable underestimated prevalence of PH in the general populations undergoing general anesthesia, these findings may have a significant effect on the management of patients with acute or chronic PH. Validation of these experimental data in clinical practice should therefore be encouraged.

The authors thank Manuel Jorge-Costa (Technical Assistant, Faculty of Medicine, University of Geneva, Geneva, Switzerland), Michèle Brunet (Technical Assistant, Faculty of Medicine, University of Geneva), and Sylvie Roulet (Technical Assistant, Faculty of Medicine, University of Geneva) for excellent technical assistance.

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