Adverse Effects of Halothane in a Canine Model of Acute Right Ventricular Hypertension

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The effects of acute right ventricular (RV) hypertension (RVH) induced by pulmonary artery (PA) constriction, and of two concentrations (mean inspired 0.8 and 1.5%) of halothane (HAL) during RVH on global and regional RV performance (ultrasound dimension technique), and on coronary hemodynamics (electromagnetic flow probes) were studied in 12 open-chest dogs anesthetized and paralyzed by continuous infusions of fentanyl and pancuronium. Following PA constriction, RV systolic pressure more than doubled, RV end-diastolic and systolic dimensions increased, and stroke volume (SV) and segment shortening fell (P all < 0.05). There was no evidence of regional myocardial dysfunction (i.e., akinesis, systolic lengthening, post-systolic shortening), and reactive hyperemia in response to right coronary artery occlusion was present. Subsequent addition of HAL (0.8%) resulted in further increases in end-diastolic and systolic dimensions, and in marked decreases in right coronary blood flow, segment shortening, SV, and aortic pressure. During HAL 1.5% (range: 1.2–1.6%), regional myocardial dysfunction developed in three animals, reactive hyperemia was abolished in five out of six animals tested, and metabolic acidosis developed. Release of PA constriction during 1.5% HAL in seven animals resulted in improved global and regional RV performance, disappearance of regional myocardial dysfunction, and restoration of reactive hyperemia. In this canine model of acute RVH, increasing concentrations of HAL led to increasing deterioration in global and regional RV performance most likely due to inadequate coronary perfusion. (Key words: Anesthetics, volatile: halothane. Circulation: right ventricle. Heart: coronary hemodynamics; regional myocardial performance; right ventricular hypertension.)

Patients with primary pulmonary hypertension, recurrent pulmonary thromboembolism, and pulmonary veno-occlusive disease also experience right ventricular (RV) hypertension (RVH). Anesthetic management of such patients is poorly documented. An inhalational anesthetic technique may be selected to enable administration of 100% O₂ if necessary, and to avoid further increases in pulmonary artery pressure. Thus, knowledge of the effects of RVH on cardiac performance, and of the interactions between inhalational anesthetics and RV performance during RVH may be helpful.

Accordingly, the aims of this study were, first, to induce RVH observing its effects on regional and global RV performance and coronary hemodynamics, and second, to subsequently study the effects of increasing concentrations of halothane (HAL) on regional and global RV performance and coronary hemodynamics during sustained RVH. Emphasis was placed on inducing a degree of RVH that would have only little adverse effects on cardiac output, global RV performance, and systemic hemodynamics, thus, simulating the patient who may clinically be asymptomatic but who, nevertheless, has hemodynamically significant RV hypertension.

Methods

INSTRUMENTATION

Twelve mongrel dogs of either sex weighing between 12 and 37 kg received intramuscular fentanyl (0.04 mg/kg) and droperidol (2 mg/kg), and were anesthetized and paralyzed with continuous iv infusions of pentobarbital (1 mg·kg⁻¹·h⁻¹), fentanyl (20 μg·kg⁻¹·h⁻¹) and pancuronium (0.04 mg·kg⁻¹·h⁻¹). Ventilation was controlled with a constant-volume ventilator (Harvard Apparatus Co, South Natick, MA). Respiratory rates were adjusted to maintain the arterial carbon dioxide tension (PaCO₂) between 30 and 40 mmHg. Tidal volume (15 ml/kg) and inspired oxygen concentration in air (approximately 50%) were kept unchanged throughout the experiment. Positive end-expiratory pressure (2 cm H₂O) was applied to prevent major airway collapse in the open-chest animals. After an initial iv bolus dose (1 mEq/kg), sodium bicarbonate (NaHCO₃) was administered by continuous iv infusion (0.5 mEq·kg⁻¹·h⁻¹) throughout the experiment in order to avoid having to correct any significant metabolic acidosis by a larger bolus dose with its subsequent acute effects on systemic, pulmonary, and coronary hemodynamics.

All dogs were in the supine position and placed on a heating element incorporated in the operating table. Body temperature (°C) was continuously monitored by a thermistor of a flow-directed thermocouple catheter (Edwards Laboratory, Model 93–134–7F) inserted through the left femoral vein and advanced into the right atrium. All animals received 4–6 ml·kg⁻¹·h⁻¹ of normal saline.

Catheter-tip manometers (6F, Millar Instruments Inc., TX) were inserted through an internal mammary artery, the left carotid artery, and the right jugular vein, and advanced into the ascending aorta, and into the left (LV) and the right ventricles (RV), respectively. Stiff polyethylene tubing (ID 1.0 mm, OD 1.6 mm) was advanced into the aortic arch via the left femoral artery. The catheter-tip manometers were calibrated as previously described.²
The chest was entered through a median sternotomy, and the heart was suspended in a pericardial cradle. Precalibrated electromagnetic flow probes (Stöutzer Mess-technik, Waldkirch, West Germany) of appropriate sizes to ensure a snug fit were placed around the main pulmonary artery (PA), the right coronary artery (RCA) approximately 1–2 cm distal to its origin, and (in 8 animals) around the left anterior descending coronary artery (LAD) distal to its first large diagonal branch. The flow probes were connected to flow meters with incorporated nonocclusive zero (Hellige Co, Freiburg, West Germany).

Regional myocardial performance was evaluated by sonomicrometry. Two pairs of piezoelectric crystals (5 MHz, 1.5–2.0 mm diameter) were inserted into the subendocardium of the inflow (longitudinal direction) and outflow tract (transverse direction) of the RV. Care was taken to ensure that the crystals in the inflow tract had been placed within the area supplied by the RCA distal to the flow probe. This was done by occluding transiently the RCA at the site of the attached flow probe and observing the area of developing tissue cyanosis.

Myocardial segment lengths (SL) between each pair of crystals were determined at end-diastole (SL_{ed}) and at the time of maximal shortening during systole (SL_{sys}). From these values, percent shortening during systole (ΔSL) was derived: ΔSL(%) = (SL_{ed} - SL_{sys})/SL_{ed} · 100. End-diastole was defined as the beginning of the sharp upslope in the expanded RV pressure or the RV dP/dt tracings, and end-systole as the moment the PA flow signal crossed the zeroline following ejection. The ultrasonic signals were also assessed visually for qualitative changes such as akinisis, paradoxical systolic segment lengthening, or post-systolic segment shortening.

**HEMODYNAMIC MEASUREMENTS**

A multichannel recorder (Hellige Co., Freiburg, West Germany) was used for the continuous recording of hemodynamic and ultrasonic signals. RV dP/dt was derived from the RV high-fidelity signal using an operational amplifier connected to a differentiator (Hellige Co., Freiburg, West Germany). RCA (CVR_{R}) and LAD (CVR_{LAD}; n = 8) vascular resistances, and stroke volume (SV) were derived from the following formulae:

\[
\text{CVR}_{R} (\text{mmHg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}) = \frac{\text{AoP}_{m} (\text{mmHg}) - \text{RVEDP} (\text{mmHg})}{\text{CBF}_{R} (\text{ml} / \text{min})}
\]

\[
\text{CVR}_{LAD} (\text{mmHg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}) = \frac{\text{AoP}_{d} (\text{mmHg}) - \text{LVEDP} (\text{mmHg})}{\text{CBF}_{LAD} (\text{ml} / \text{min})}
\]

\[
\text{SV} (\text{ml}) = \frac{\text{PAF} (\text{ml} / \text{min})}{\text{HR} (\text{beats/min})}
\]

where AoP_{m} = mean aortic pressure, RVEDP = right ventricular end-diastolic pressure, PAF = mean pulmonary artery flow, CBF = mean right (R) and left anterior descending (LAD) coronary artery blood flow, LVEDP = left ventricular end-diastolic pressure, and HR = heart rate (as derived from the R-R intervals of an extremity ECG). AoP_{d}, AoP_{m}, RVEDP, RV systolic pressure (RVSP), systolic aortic pressure (AoP_{a}), and LVEDP were all determined by catheter-tip manometers.

**EXPERIMENTAL PROTOCOL**

After the sternotomy and catheter insertion, pentobarbital was discontinued, and no further pentobarbital was administered for approximately 2 h prior to the start of the experiment. Additional bolus of fentanyl (10 μg/kg) were administered as indicated by increases in HR and blood pressure or movement of the animal. At the end of the surgical preparation, at least 30 min were allowed for stabilization. Hemodynamic and regional myocardial function variables, body temperature (T), hematocrit (Hct; Microcentrifuge Compur, Model M1100), arterial blood gases, and arterial pH (Instrumentation Laboratory, Model 613) were recorded at the end of each experimental period.

After control readings (C) had been obtained, acute RV hypertension (RVH) was induced by gradually constricting the main PA by means of a snare placed around the main PA distal to the flow probe. The snare was tightened until RVSP had approximately doubled. After stabilization of RVH (at least 20 min after induction of RVH) the measurements were repeated. HAL was then administered through a precalibrated vaporizer (Flucotec 3, Cpraen, England) at inspired concentrations of first 0.8% (HAL₁) and subsequently 1.6% (HAL₂). In four animals, however, the inspired concentration at HAL₂ was reduced to 1.2% when there was no evidence of beginning hemodynamic stabilization at a mean AoP_{d} of approximately 50 mmHg. The respective measurements at HAL₁ and HAL₂ were made after hemodynamic stabilization. With the introduction of HAL, the rate of fentanyl infusion was reduced by approximately 30% to 15 μg · kg^{-1} · min^{-1}.

In seven animals following HAL₂, the PA constriction was released, inspired HAL concentration was kept constant, and the measurements were repeated after hemodynamic stabilization (HAL₂ ⪿ RVH).

In six animals, peak reactive hyperemic flow (PRHF) was determined following a 10-s occlusion of the RCA during C, RVH, HAL₁, and HAL₂ ⪿ RVH.

**STATISTICAL ANALYSIS**

The data were statistically analyzed by Friedman's statistic followed by Wilcoxon signed-rank test where appropriate. P < 0.05 was considered statistically significant.
Results

Effects of PA Constriction (Table 1)

Acute PA constriction resulted in increases in RVSP, RV dp/dt, and RVEDP. In the RV inflow (RVIT) and outflow tracts (RVOT), systolic (RVITSLSys, RVOTSLsys) as well as end-diastolic dimensions (RVITSLed, RVOTSLed) increased, and segment shortening (ARVITSL, ARVOTSL) decreased. There was no evidence of regional paradoxical systolic lengthening or postsystolic shortening. PAF did not change significantly due to a marked increase (34%) in HR. However, SV fell by more than 30%. There was a small (8%) but significant decrease in AoPm. LVEDP remained unchanged.

As for the right coronary circulation, there were marked increases in CBF (73%) and in CBF per heart beat (27%), and a decrease in CVR (46%). In contrast, as for the left coronary circulation, CBF and CVR remained unchanged, and CBF per heart beat decreased (27%). PaO2, PaCO2, T, and pH did not change significantly. There was a small (8%) rise in Hct.

Effects of HAL during PA Constriction (Table 1)

There were dose-related decreases in RVSP, RV dp/dt, regional systolic shortening (ARVITSL, ARVOTSL), SV and PAF, and dose-related increases in systolic dimensions (RVITSLsys, RVOTSLsys). End-diastolic pressure (RVEDP) and dimensions (RVITSLed, RVOTSLed) increased only at the higher concentration of HAL (HAL2).

At HAL1, there was no evidence of regional myocardial dysfunction. At HAL2, however, akinesia, and/or para-

### Table 1. Parameters of Circulation, Regional Myocardial Function, Respiration, and General Homeostasis during Various Experimental Periods

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 12)</th>
<th>RVH (n = 12)</th>
<th>HAL1 (n = 12)</th>
<th>HAL2 (n = 12)</th>
<th>HAL2 + RVH (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV hemodynamics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RVITSLsys (mm)</td>
<td>10.5 ± 0.5</td>
<td>11.0 ± 0.6†</td>
<td>10.9 ± 0.5</td>
<td>11.5 ± 0.6†</td>
<td>10.8 ± 0.7*</td>
</tr>
<tr>
<td>RVOTSLsys (mm)</td>
<td>8.1 ± 0.5</td>
<td>9.0 ± 0.6†</td>
<td>9.4 ± 0.5†</td>
<td>10.3 ± 0.6†</td>
<td>9.2 ± 0.7*</td>
</tr>
<tr>
<td>ARVITSL (%)</td>
<td>21.7 ± 1.3</td>
<td>18.7 ± 1.8*</td>
<td>14.1 ± 1.7†</td>
<td>10.6 ± 1.6†</td>
<td>15.1 ± 2.0*</td>
</tr>
<tr>
<td>RVOTSLed (mm)</td>
<td>10.8 ± 0.6</td>
<td>11.8 ± 0.8†</td>
<td>12.8 ± 0.8‡</td>
<td>12.5 ± 0.8‡</td>
<td>11.8 ± 0.9*</td>
</tr>
<tr>
<td>ARVOTSL (%)</td>
<td>8.6 ± 0.5</td>
<td>9.8 ± 0.7‡</td>
<td>11.2 ± 0.8‡</td>
<td>11.2 ± 0.8‡</td>
<td>10.2 ± 0.9*</td>
</tr>
<tr>
<td>RVEDP (mmHg)</td>
<td>20.3 ± 1.7</td>
<td>17.1 ± 1.8*</td>
<td>15.3 ± 1.5†</td>
<td>10.5 ± 1.5†</td>
<td>13.8 ± 1.9*</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>3.0 ± 0.2</td>
<td>4.2 ± 0.2†</td>
<td>4.0 ± 0.3</td>
<td>4.6 ± 0.3†</td>
<td>4.0 ± 0.3*</td>
</tr>
<tr>
<td>RV dp/dt (mmHg/s)</td>
<td>22 ± 1</td>
<td>49 ± 2†</td>
<td>38 ± 1†</td>
<td>31 ± 2†</td>
<td>18 ± 2*</td>
</tr>
<tr>
<td>PAF (l/min)</td>
<td>2.2 ± 0.1</td>
<td>2.0 ± 0.2</td>
<td>1.6 ± 0.1†</td>
<td>1.1 ± 0.1†</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>21 ± 2</td>
<td>14 ± 1†</td>
<td>12 ± 1†</td>
<td>9 ± 1†</td>
<td>13 ± 2*</td>
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<tr>
<td>HR (/min)</td>
<td>105 ± 5</td>
<td>141 ± 5†</td>
<td>135 ± 5</td>
<td>124 ± 5*</td>
<td>99 ± 6*</td>
</tr>
<tr>
<td>Coronary hemodynamics</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CBF (ml/min)</td>
<td>15 ± 1</td>
<td>26 ± 2†</td>
<td>19 ± 1†</td>
<td>13 ± 1†</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>CBF (ml/l/beat)</td>
<td>145 ± 10</td>
<td>184 ± 13†</td>
<td>140 ± 9†</td>
<td>108 ± 11†</td>
<td>124 ± 14*</td>
</tr>
<tr>
<td>CBF (ml/kg - ml⁻¹ -min)</td>
<td>6.7 ± 0.4</td>
<td>3.6 ± 0.3†</td>
<td>3.6 ± 0.3</td>
<td>4.2 ± 0.6</td>
<td>5.3 ± 0.7*</td>
</tr>
<tr>
<td>CBF (ml/kg - ml⁻¹ -min)</td>
<td>25 ± 3</td>
<td>25 ± 3</td>
<td>21 ± 2†</td>
<td>15 ± 2†</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>CBF (ml/kg - ml⁻¹ -min)</td>
<td>243 ± 29</td>
<td>177 ± 18†</td>
<td>154 ± 15*</td>
<td>127 ± 17†</td>
<td>176 ± 26*</td>
</tr>
<tr>
<td>CBF (ml/kg - ml⁻¹ -min)</td>
<td>3.8 ± 0.5</td>
<td>3.7 ± 0.5</td>
<td>3.6 ± 0.6</td>
<td>3.5 ± 0.6</td>
<td>3.2 ± 0.6</td>
</tr>
<tr>
<td>LV and systemic hemodynamics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AoPm (mmHg)</td>
<td>100 ± 3</td>
<td>92 ± 4*</td>
<td>69 ± 3†</td>
<td>52 ± 3†</td>
<td>67 ± 3*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>6.0 ± 0.4</td>
<td>5.5 ± 0.5</td>
<td>5.5 ± 0.5</td>
<td>6.0 ± 0.5</td>
<td>6.9 ± 0.6*</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.41 ± 0.01</td>
<td>7.42 ± 0.01</td>
<td>7.37 ± 0.01†</td>
<td>7.31 ± 0.01†</td>
<td>7.35 ± 0.01*</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>34 ± 1</td>
<td>35 ± 1</td>
<td>34 ± 1</td>
<td>34 ± 1</td>
<td>35 ± 1</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>256 ± 20</td>
<td>239 ± 20</td>
<td>205 ± 18*</td>
<td>176 ± 15*</td>
<td>210 ± 21*</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>34 ± 2</td>
<td>36 ± 2*</td>
<td>35 ± 2</td>
<td>34 ± 2</td>
<td>33 ± 2</td>
</tr>
<tr>
<td>T (°C)</td>
<td>37.3 ± 0.2</td>
<td>37.5 ± 0.2</td>
<td>37.6 ± 0.2</td>
<td>37.7 ± 0.2</td>
<td>37.5 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE.
RVH = right ventricular (RV) hypertension. HAL1 and HAL2 = inspired halothane concentrations of 0.8 and 1.6%, respectively. HAL2 + RVH = HAL1 without RVH (i.e., after release of pulmonary artery constriction). IT = inflow tract. SL = (myocardial) segment length. ED = end-diastolic. SYS = systolic. ΔSL = systolic SL shortening. OT = outflow tract. RVEDP = RV end-diastolic pressure. RVSP = RV systolic pressure. PAF = mean pulmonary artery flow. SV = stroke volume. CBF = mean right (R) and left anterior descending (LAD) coronary blood flow. CVR = right (R) and left anterior descending (LAD) coronary vascular resistance. AoPm = mean aortic pressure. LVEDP = left ventricular end-diastolic pressure. Hct = hematocrit. T = temperature. * † = P < 0.05 (*) or < 0.01 (†) when compared to preceding value. During Control, RVH, HAL1 and HAL2, values for CBF and CVR were determined in eight animals only.
doxical systolic lengthening, and/or postsystolic shortening developed in the RVIT and RVOT in three animals. There was a dose-related decline in AoPr (43% at HAL2), with no significant change in LVEDP.

There were dose-related decreases in CBFR of approximately 25% and 45% at HAL1 and HAL2, respectively. CVRFR did not change significantly. Changes in the left circulation were qualitatively similar, but quantitatively less pronounced.

Whereas PaCO2, Hct, and T were little affected, there was a continuous decline in pH and PaO2.

**EFFECTS OF RELEASE OF PA CONTRACTION DURING HAL2 (TABLE 1)**

Regional systolic shortening (ΔRVITSL, ΔRVOTSL) and SV increased by 30–45%. PAF did not increase significantly due to a decrease in HR. End-diastolic pressure (RVEDP) and dimensions (RVITSLred, RVOTSLred), and systolic dimensions (RVITSLsys, RVOTSLsys), RVSP and RV dP/dt all fell. Akinesia, systolic lengthening, and postsystolic shortening disappeared. AoPr and LVEDP increased.

In both right and left coronary circulation, CBFR did not change significantly. However, due to the decrease in HR, CBF per heart beat increased. CVRFR increased, CVRLab remained unchanged. Release of the constriction was associated with increases in pH and PaO2.

**PEAK REACTIVE HYPEREMIC FLOW RESPONSES (TABLE 2)**

During the control state (C), peak reactive hyperemic flow (PRHF) following a 10-s occlusion of the RCA was 207% (range 160–275%) above baseline flow. PRHF decreased to 46% (range 20–85%) above baseline flow during RVH. During HAL2, PRHF was abolished in five of the six animals tested. It exceeded baseline flow by 26% in only one of these animals. Following the release of the PA constriction, PRHF response increased again to 67% (range 36–100%) above baseline flow.

**Discussion**

This canine model of acute PA constriction resulted in moderate RV hypertension with evidence of impaired systolic performance. Addition of increasing concentrations of HAL resulted in progressive deterioration of RV function to which RV ischemia might have contributed.

**CRITIQUE OF METHODS**

Although the protocol was designed to simulate a clinical situation in which patients with elevated RV afterload receive a HAL anesthetic, it needs to be emphasized that the observed pathophysologic events are relevant only to acute RV hypertension and may, thus, be different in conditions of chronic RV hypertension and hypertrophy. Mechanical obstruction of the main PA was used to induce RV hypertension. This subjects the RV to a different and greater dynamic afterload than a comparable (more distal) microvascular lung injury induced by emboli. However, with experimental pulmonary emboli, RV afterload may change with time. In contrast, mechanical constriction of the proximal PA maintains PA obstruction constant throughout the experiment. It is, thus, unlikely that changes in RV function occurred on the basis of changes in RV afterload.

This study was performed in preparations with an open pericardium because this facilitates placement of piezoelectric crystals and electromagnetic flow probes. In the thin-walled RV, the pericardium may influence RV function during increased pressure loads. However, in the experimental animal as well as in humans, the pericardium exerts little measurable effect when filling pressures are less than 10 mmHg. In the present study, RV filling pressures remained well below this value throughout. Even at RVEDP as high as 10 mmHg, the pericardium has been shown to exert an only moderate restraint on cardiac dilation. When the same degree of acute RVH was induced in the presence of an intact pericardium, the functional and hemodynamic responses were very similar to the ones reported here: segment shortening of RV inflow and outflow tract, and SV fell, and CBFR increased markedly. In contrast to the present study, end-diastolic segment lengths did not increase, but neither did RVEDP. In a further investigation on the hemodynamic and myocardial blood flow responses to an acute increase in RVSP, only RVEDP differed significantly between animals with an opened and a closed pericardium. It is thus possible that had the pericardium remained

<table>
<thead>
<tr>
<th>TABLE 2. Flow Responses to Right Coronary Artery Occlusion (n = 6)</th>
</tr>
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<tr>
<td></td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>B</td>
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<tr>
<td>15 ± 2</td>
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</tbody>
</table>

Values in ml/min (means ± SE).

B = baseline value. PRHF = peak reactive hyperemic flow. (See table 1 for further abbreviations.)
HALOTHANE AND RIGHT VENTRICULAR HYPERTENSION

RV PERFORMANCE DURING PA CONSTRUCTION

PA constriction markedly increases RV afterload.\(^5\) Since the thin-walled RV is extremely sensitive to an acute increase in afterload,\(^17,18\) compensatory increases in preload and contractility are required to maintain RV output.

As expected,\(^17,18\) indices of preload (end-diastolic dimensions and pressure) increased. An even greater increase in preload might have been counteracted by 1) the increase in HR which tends to decrease cardiac size;\(^19\) and 2) a positive inotropic effect secondary to an increase in contraction frequency,\(^19\) homeometric autoregulation,\(^20\) or a reflex increase in cardiac sympathetic nerve activity\(^21\) in response to a fall in systemic pressure.

Despite marked increases in RVSP and RV dP/dt, pump function (regional myocardial shortening, SV) declined. This is consistent with previous experimental data which show that the extent of RV shortening and SV are inversely related to RV afterload,\(^17\) and that an acute increase in RV afterload may impair systolic performance unrelated to reductions in preload or contractility.\(^22\) Analysis of PA flow tracings confirmed previous findings that reduction in SV during increased RV load resistance is caused primarily by a reduction in peak flow and by a shortening of the ejection period.\(^23\) The increase in systolic segment lengths indicate that systolic volumes had increased. It has previously been shown that in the isolated perfused heart, RV systolic volume increases as pressure opposing ejection is raised.\(^24\) In addition, in the presence of maintained preload, an increase in HR will raise systolic dimensions.\(^19\)

Several investigators have previously studied the hemodynamic response to acute PA obstruction.\(^5,25-27\) Results are difficult to compare because of differences in baseline sympathetic tone (elevated vs. normal as reflected by baseline HR and blood pressure), in the state of wakefulness (awake vs. anesthetized), in the experimental model (closed-chest vs. open-chest), in the kind of baseline anesthesia (pentobarbital vs. chloralose/morphine vs. fentanyl/droperidol/N₂O), and in the degree of PA constriction. Nevertheless, at comparable increases in RVSP of approximately 100%, elevation in RVEDP, RV end-diastolic and end-systolic volumes;\(^26\) and remarkably similar increases in end-diastolic and systolic segment lengths and reductions in segment shortening of inflow and outflow tract\(^27\) have been reported.

CORONARY PERFUSION DURING PA CONSTRUCTION

The increase in CBF\(_R\) and the decrease in CVR\(_R\) following PA constriction are most likely due to the increase in myocardial oxygen consumption (MV\(_O_2\)) associated with the increases in afterload, preload, and HR.\(^28-30\) The increase in CBF\(_R\) per heart beat by almost 30% is evidence that the increase in CBF\(_R\) was not solely due to the rise in HR.

Since impedance to myocardial blood flow is determined by the dynamic interaction of perfusion pressure, vasomotor tone, and extravascular forces acting on the intramural coronary vessels,\(^31\) it was to be expected that the decrease in the systolic aortic-RV pressure gradient (table 3) and the simultaneous increase in extravascular myocardial compression (due to increases in RVSP, RV dP/dt, and HR) would reduce coronary vasodilator reserve and systolic myocardial perfusion. In accordance with previous data,\(^32,33\) (when compared to the control state) reactive hyperemia (table 2) was clearly reduced (indicating reduced coronary vascular reserve), and (from analysis of phasic coronary flow recordings) augmentation in CBF\(_R\) occurred primarily during diastole (indicating systolic impedance to flow). However, increased RVSP, little reduction (approximately 15%) in regional systolic shortening, lack of regional myocardial dysfunction, and the increase in CBF\(_R\) per heart beat would all suggest that the well-maintained diastolic aortic-RV pressure gradient (table 3) and the compensatory decrease in CVR\(_R\) ensured adequate RV perfusion despite reduced coronary vasodilator reserve and impaired systolic perfusion.
Table 3. Aortic-Right Ventricular Pressure Gradients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>RVH</th>
<th>HAL1</th>
<th>HAL2</th>
<th>HAL4 + RVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>AopPₚ - RVSP (mmHg)</td>
<td>96 ± 3</td>
<td>58 ± 3†</td>
<td>47 ± 3†</td>
<td>37 ± 2†</td>
<td>65 ± 3*</td>
</tr>
<tr>
<td>AopPₚ - RVEDP (mmHg)</td>
<td>85 ± 3</td>
<td>80 ± 4</td>
<td>56 ± 3†</td>
<td>39 ± 2‡</td>
<td>54 ± 3*</td>
</tr>
<tr>
<td>AopPₚ - RVEDP (mmHg)</td>
<td>97 ± 3</td>
<td>88 ± 4*</td>
<td>65 ± 3†</td>
<td>45 ± 3†</td>
<td>65 ± 3*</td>
</tr>
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Values are means ± SE.
AopPₚ, AopPₚ = systolic (s) and diastolic (d) aortic pressure. Control,

In the left coronary circulation, mean CBF₉AD remained unchanged due to the increase in HR. This is reflected by the substantial decrease in CBF₉AD when expressed per heart beat. Such a decrease may be related to reductions in systolic and mean Aop, in SV, and to the tendency for a fall in LVEDP resulting in a net reduction of LV MVO₂. Similar findings have been reported previously.²⁴⁻²⁷ Since α-adrenergic blockade improves LV perfusion during RV pressure overload,²⁵ it is conceivable that some degree of α-adrenergic receptor-mediated vasoconstriction is present.

RV Performance during PA Constriction and HAL

The addition of HAL to pre-existing PA constriction caused a dose-related, progressive deterioration in global and regional RV performance. The marked reductions in RVSP, RV dP/dt, SV, and segmental shortening, and the increase in systolic dimensions, despite unchanged PA constriction (afterload) and elevated end-diastolic dimensions and pressure (preload), reflect the negative inotropy of HAL. This is in accordance with previous studies in closed-chest animals.²⁸⁻³⁰ Of greater concern, however, is the occurrence of regional contraction patterns that are associated with myocardial ischemia such as akinesis, systolic bulging, and post-systolic shortening.¹³ Thus, the decrease in global RV pump function may not have been purely the result of the negative inotropy of HAL but may in part be attributable to inadequate myocardial perfusion. Development of metabolic acidosis and the fall in PaO₂, reflect increasingly insufficient body perfusion.

Coronary Perfusion during PA Constriction and HAL

The behavior of the coronary circulation during PA constriction and HAL suggests the hypothesis that part of the decline in RV performance was based on inadequate coronary perfusion. Absence of reactive hyperemia in five out of six animals tested indicates that coronary vascular reserve was exhausted and that the vascular bed of the RCA was maximally dilated. This does, in fact, suggest that the RV was inadequately perfused.

Inadequate myocardial perfusion during HAL₂ is further suggested by the fact that when compared to control values, CBF₉ per heart beat had declined by 25% despite significantly elevated indices of MVO₂ (i.e., end-diastolic dimensions and pressure, RVSP, RV dP/dt, HR). Insufficient coronary perfusion during HAL₂ is likely to have been caused by the combination of: 1) increased extravascular compressive forces during systole (elevated RVSP, RV dP/dt, systolic dimensions) and diastole (elevated end-diastolic dimensions and pressures); 2) shortened diastolic filling time (elevated HR); 3) markedly decreased systolic (AopPₚ - RVSP) and diastolic (AopPₚ - RVEDP) aortic-RV perfusion gradients (table 3); and 4) the lack of any further compensatory decrease in CVR₉. Analysis of phasic coronary flow recordings during HAL₂ revealed that CBF₉ no longer predominated during diastole as it did during initial PA constriction. This is most likely the result of a decrease in the diastolic aortic-RV pressure gradient by 50% and increased impedance to diastolic myocardial perfusion caused by elevated end-diastolic dimensions and pressure. This is in agreement with previous findings showing that attenuation of right coronary vasodilator reserve and reduction in coronary perfusion is most pronounced in the RV subendocardial layers.⁶⁻⁴⁰⁻⁴¹

The results indicate that during RVH, the likely decrease in MVO₂ following the administration of HAL (due to its negative inotropic and chronotropic effects) was outweighed by the concomitant decrease in myocardial O₂ supply (due to reduced aortic-RV perfusion gradients and increased impedance to myocardial perfusion). This re-emphasizes the utmost importance of adequate coronary perfusion pressure in the presence of an increased RV afterload.⁶⁻⁴²⁻⁴³ It is conceivable, however, that HAL actually prevented even worse deterioration of RV performance by reducing MVO₂ at a time of impaired myocardial perfusion. By that reasoning, at equally low coronary perfusion pressures, a pure peripheral vasodilator without concomitant myocardial-depressant effect might have caused an even greater degree of RV functional impairment.

The behavior of the left coronary circulation (decrease in CBF₉AD, unchanged CVR₉) reflects the likely decrease in LV MVO₂ (due to the negative inotropic and chronotropic effects of HAL) and the decrease in systemic perfusion pressure.⁵¹
RELEASE OF PA CONSTRUCTION DURING HAL

Release of PA constriction during unchanged inspired concentrations of HAL resulted in a marked improvement in global and regional RV performance. This indicates that the preceding deterioration in RV function was not caused primarily by the negative inotropic effects of HAL, but rather by the combination of increased RV afterload (PA constriction) and concomitant myocardial depression (HAL).

Despite the persistent (myocardial-depressant) effects of HAL, end-diastolic and systolic dimensions decreased, SV and segment shortening increased, and regional myocardial dysfunction disappeared entirely. Improvement in global perfusion is reflected by increases in pH and PaO2. The myocardial-depressant effects of HAL per se become evident when values determined after the release of PA constriction are compared to those during the control state (lower RVSP, RV dp/dt, SV, and systolic shortening despite unchanged RV afterload and HR and increased indices of RV preload).

Despite reductions in indices of MVO2 following the release of PA constriction (decreases in RVSP, RV dp/dt, end-diastolic and systolic dimensions, HR), mean CBF remained unchanged, and CBF per heart beat even increased. Reappearance of reactive hyperemia in each of six animals tested indicates restored coronary vascular reserve. Improved myocardial perfusion is likely to have been the result of increased (40–75%) systolic and diastolic aortic-RV pressure gradients (table 3), and reduction in impedance to coronary flow. The increase in CVR is evidence that a compensatory decrease in coronary vasomotor tone was no longer required to ensure adequate coronary perfusion.

In this canine model of acute RV hypertension, increasing concentrations of HAL led to progressive deterioration in global and regional RV performance. Regional myocardial dysfunction and absence of reactive hyperemia during HAL2 are evidence that RV ischemia might have contributed to the deterioration in RV function. Since RV performance becomes increasingly dependent on adequate coronary perfusion pressure, myocardial depressant anesthetics such as HAL must be used with great caution during an elevated RV afterload.

The author wishes to thank Joanne Gale and Jürgen Maertens for their expert technical assistance, and Sarah Nevill and Gunda Steinert for her valuable secretarial support.

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