Influence of Hypertension on MAC of Halothane in Rats

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This study was designed to assess the relationship between MAC and hypertension. To this purpose, MAC of halothane was determined in fully inbred spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY). Because MAC determination was performed in animals whose lungs were mechanically ventilated, the adequacy of the ventilation was initially established in 20 rats equally divided into SHR and WKY, and instrumented with catheters in the abdominal aorta. Subsequently, MAC of halothane was determined in 40 rats equally divided into SHR and WKY, including those instrumented. There were no differences in MAC of halothane between SHR (n = 20) and WKY (n = 20) (1.08 ± 0.02% vs. 1.11 ± 0.02%). Subgroup analysis indicated that MAC of halothane was not affected by the presence of an arterial catheter in the abdominal aorta (SHR 1.09 ± 0.06% vs. 1.08 ± 0.02%; WKY 1.15 ± 0.04% vs. 1.08 ± 0.02%). The authors' data provide experimental evidence that MAC is not affected by either chronic hypertension or limited instrumentation. (Key words: Anesthetics, volatile: halothane. Hypertension. Potency, anesthetic: MAC.)

The determination of minimum alveolar concentration (MAC) of inhalational anesthetics has been a valid tool for studying the influence of various drugs and (patho-)physiologic conditions on anesthetic requirements. It has been clearly established that MAC is dependent on age,1 body temperature,2 and to a lesser extent, on arterial oxygen content and acid-base status.3 Evidence supports the concept that central nervous system-mediated hypertension may also affect MAC. Mephenetermine and ephedrine—drugs that stimulate the release of catecholamines from the brain—increase MAC of halothane by 21 and 50%, respectively.4 In addition, stimulation of opiate5 and α2 receptors6 in the brain, as well as inhibition of calcium and/or sodium movement through voltage-dependent channels,7 have been demonstrated to decrease MAC for halothane. These same neurophysiologic factors also have been involved in the development of hypertension. In spontaneously hypertensive rats (SHR) an increase in the number of k opiate and dihydropyridine calcium channel receptors have been found in the hypothalamus, the cortex, and the hippocampus, respectively.8–9 Hypertension has been also associated with a decrease in α2 receptors in the vagus, the solitary tract, the hypothalamus, and the thalamus.10

The properties of inhalational anesthetics have been proven to be different in SHR as compared with their normotensive controls.11 The significance of these differences is based on the assumption that MAC is not affected by blood pressure. Since there is suggestive evidence against this concept, we decided to compare MAC of halothane in SHR versus normotensive Wistar Kyoto rats (WKY).

Methods

The protocol was approved by the Baylor College of Medicine and the University of Houston Animal Care Committees. All animals used in this study were maintained in a temperature-controlled environment with food and water ad libitum and a 12-h light/dark cycle.

Validation of Experimental Conditions

In 20 rats, ten SHR and ten WKY (WKY, a genetic normotensive counterpart), a preliminary study was performed to establish that animals were normocapnic and normoxic during mechanical ventilation. Under halothane anesthesia all animals were chronically instrumented with a silastic catheter in the abdominal aorta to allow for arterial blood gas sampling. At least 7 days after surgery, when the animals had recovered from surgery and acclimated to the laboratory, an arterial blood sample (0.2 ml in capillary tubes) was withdrawn from the conscious animals and analyzed for P02, PCO2, and pH. The rats were then placed in a transparent container (Harvard Apparatus, South Natick, MA) through which air containing 5% halothane was passed at a flow rate of 3 l/min for induction of anesthesia. One minute following loss of righting reflex, the tracheas were quickly intubated and the lungs mechanically ventilated at about 60 breaths per min and a volume of 0.9–1 ml/100 g (Harvard Apparatus) with a gas mixture containing halothane 1.3%, oxygen, and air at an inspired oxygen concentration of 25–28%. Rectal temperature was continuously monitored with a
thermocouple probe (Yellow Springs Instruments, Yellow Springs, OH) and maintained at 37°C with a heating pad (Harvard Apparatus) and heating lamp when necessary. End-tidal gas samples were obtained with an airtight glass syringe during 10–20 expirations at a sample port immediately proximal to the endotracheal tube. These samples were analyzed for end-tidal carbon dioxide (Lifespan 100, Biochem International Inc., Waukesha, WI) and anesthetic concentration, using infrared absorption techniques (Beckman LB-2, Beckman Inc., Schiller Park, IL). Simultaneously, arterial blood samples were analyzed for PaO₂, PaCO₂, and pH. End-tidal to arterial PCO₂ differences were then calculated.

**DETERMINATION OF MAC IN SHR AND WKY**

Twenty male SHR and 20 sex- and age-matched WKY (Harlan Sprague-Dawley, Indianapolis, IN; age 14–16 weeks, weight 275–325 g), including five instrumented (protocol A) SHR and five WKY were studied. All MAC determinations were performed and completed between 10:00 A.M. and 4:00 P.M. The rats were anesthetized, the tracheas intubated, and the lungs ventilated as described in protocol A. Rectal temperature was maintained at 37°C throughout the experiment. At least 45 min following induction of anesthesia, MAC determinations were performed as described by White et al.¹ Briefly, when end-tidal anesthetic and CO₂ concentrations in three consecutive samples taken within 15 min did not differ by more than 0.03% and 3 mmHg, respectively, a 6-inch hemostat was applied to the rat’s tail for 1 min to full ratchet lock. Gross purposeful movements of the head, body, or extremities were considered to be positive responses. When a positive response occurred, halothane concentration was increased by 10% of the preset value and the stimulus was repeated after 15 min of stable end-tidal concentration. When no response was initially noted, the concentration was decreased by 10% and the stimulus reapplied. Subsequent tail clamping was always performed proximal to a previous clamping site. MAC was calculated as the value midway between the concentration preventing and eliciting movement in response to the tail clamp.

**Table 1. Arterial Blood Gases and ETCO₂ in Awake and Halothane-Anesthetized Rats**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Awake</th>
<th>Halothane</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (mmHg)</td>
<td>90 ± 3</td>
<td>110 ± 3</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>34 ± 1</td>
<td>33 ± 1</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/l)</td>
<td>29 ± 1</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.01</td>
<td>7.39 ± 0.01</td>
</tr>
<tr>
<td>ETCO₂ (mmHg)</td>
<td>27 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SEM.

**Table 2. Effects of Instrumentation on MAC of Halothane in SHR and WKY**

<table>
<thead>
<tr>
<th>Instrumentation</th>
<th>SHR</th>
<th>WKY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninstrumented</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Instrumented</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean ± SEM.

Between (SHR vs. WKY) and within (noninstrumented vs. instrumented) group, comparisons were analyzed using unpaired t tests. Data are presented as mean ± SEM.

**Results**

**VALIDATION OF EXPERIMENTAL METHODS**

Arterial blood gases and ETCO₂ obtained in awake and anesthetized rats are presented in table 1. The data indicate that ventilation was adequate for maintaining normocapnia and normoxia.

**MAC IN SHR AND WKY**

MAC of halothane in SHR and WKY was essentially the same (1.08 ± 0.02% vs. 1.11 ± 0.02%). The means approximate those described by White et al. for Sprague-Dawley rats.¹ In addition, instrumentation did not affect MAC values in either SHR or WKY (table 2).

**Discussion**

Our data demonstrate that normoxia and normocapnia can be maintained during anesthesia and mechanical ventilation in rats.

Under these conditions, there was no difference in MAC of halothane between SHR and WKY. Pain threshold has been reported to be higher in SHR¹² and in patients with essential hypertension.¹³ In contrast to pain threshold, which relates to the minimal effective dose to prevent responses to painful stimuli, MAC is a well-defined response to a supramaximal painful stimulus after loss of consciousness in the presence of an anesthetic. Therefore our data do not necessarily contradict those previously reported on the effect of hypertension on pain threshold.

MAC is often used as a measure of equipotency of inhalational anesthetics in instrumented animals. It is assumed that instrumentation does not affect MAC. Our data provide experimental evidence supporting this concept. However, it should be recognized that the data were obtained from chronically instrumented animals and do not apply to the effects of acute surgical stress on MAC. Hypertension is a multifactorial and polymorphic disease. SHRs are recognized as a model for essential hy-
pertension,14 the most frequent form of hypertension in humans. Our experimental design did not include other models of hypertension because we believed that SHR are the most appropriate model for the following reasons: first, SHRs represent a model of hypertension in which central nervous system-mediated mechanisms have been involved,8–10 and there is no doubt that the central nervous system plays an essential role in anesthetic requirements; second, other human forms of hypertension, including pheochromocytoma, hyperaldosteronism, hyperthyroidism, and renal artery stenoses, etc., are mostly dependent on hormones and circulating factors. Steffey and Eger4 demonstrated that peripheral vasoconstriction does not affect MAC of halothane.

In conclusion, our data suggest that the presence of sustained hypertension and limited instrumentation does not influence anesthetic requirements for halothane.

References

11. Seyde WC, Durieux ME, Longenecker DE: The hemodynamic response to isoflurane is altered in genetically hypertensive (SHR), as compared with normotensive (WKY), rats. ANESTHESIOLOGY 66:798–804, 1987