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Determination of Minimum Alveolar Concentration for Isoflurane and Sevoflurane in a Rodent Model of Human Metabolic Syndrome

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Abstract

Background—Morbid obesity affects the pharmacokinetics and pharmacodynamics of anesthetics, which may result in inappropriate dosing. We hypothesized that obesity significantly alters the minimum alveolar concentration (MAC) for isoflurane and sevoflurane. In order to test this hypothesis, we used a rodent model of human metabolic syndrome developed through artificial selection for inherent low aerobic capacity runners (LCR) and high aerobic capacity runners (HCR). The LCR rats are obese, display phenotypes homologous to those characteristic of human metabolic syndrome, and exhibit low running endurance. In contrast, HCR rats have high running endurance and are characterized by improved cardiovascular performance as well as overall health.

Methods—Male and female LCR (n=10) and HCR (n=10) rats were endotracheally intubated and maintained on mechanical ventilation with either isoflurane or sevoflurane. A bracketing design was used to determine MAC; sensory stimulation was induced by tail-clamping. An equilibration period of 30 minutes was provided before and between the consecutive tail clamps. Two-tailed parametric (unpaired t-test) and nonparametric (Mann-Whitney test) statistical tests were used for the comparison of MAC between LCR and HCR rats. The data are reported as mean $\pm$ standard deviation along with the 95% confidence interval. A p-value of <0.05 was considered statistically significant.

Results—The MAC for isoflurane in LCR rats ($1.52\% \pm 0.13$) was similar to previously reported isoflurane-MAC for normal rats ($1.51\% \pm 0.12$). The HCR rats showed a significantly higher isoflurane-MAC ($1.90\% \pm 0.19$) as compared to the LCR rats ($1.52\% \pm 0.13$) ($p = 0.0001$). The MAC for sevoflurane was not significantly different between LCR and HCR rats and was similar to the previously published sevoflurane-MAC for normal rats ($2.4\% \pm 0.30$). There was no influence of sex on the MAC of either isoflurane or sevoflurane.

Conclusion—Obesity and associated co-morbidities do not affect anesthetic requirements as measured by MAC in a rodent model of metabolic syndrome. By contrast, high aerobic capacity is associated with a higher MAC for isoflurane and may be a risk factor for subtherapeutic dosing.

Introduction

There is an increasing concern for the potential complications involving anesthetic interventions in morbidly obese patients.¹ An effect of increased body mass index (BMI) on anesthetic pharmacokinetics has been shown.² Increased adiposity complicates the assessment of anesthetic requirements and creates the possibility of subtherapeutic anesthesia, which is considered to be a primary cause of intraoperative awareness with explicit recall.^{3,4} Intraoperative awareness remains a feared complication of surgery and is associated with a high incidence of posttraumatic stress disorder.⁵ A number of risk factors have been suggested for this complication,³ including obesity.⁶ However, a retrospective study of intraoperative awareness questioned the role of obesity as a risk factor,³ but there are no data regarding anesthetic requirements as measured by minimum alveolar concentration (MAC) in this population.

Obesity is associated with co-morbidities such as diabetes and cardiovascular disease, which together are features of human metabolic syndrome.^{7,8} A rodent model of metabolic syndrome has been generated that is characterized primarily by low aerobic oxidative capacity,^{9,10,11} obesity, and risks for complex diseases.¹² In brief, rats from a founder population of genetically heterogeneous rats (N:NIH stock) were artificially selected to diverge into two distinct lines: inherent high aerobic capacity runners (HCRs) and inherent

low aerobic capacity runners (LCRs).⁹ As compared to HCR rats, the LCR rats show increased levels of visceral fat, plasma triglycerides, plasma free fatty acids, fasting insulin levels as well as higher blood pressure and impaired glucose tolerance (Table 1).¹² This is consistent with the literature that aerobic exercise capacity shows a strong negative correlation with the occurrence of morbidities including obesity, diabetes and cardiovascular disease.¹³

We used this contrasting animal model system to test the hypothesis that the MAC of isoflurane and sevoflurane varies significantly as a function of maximal oxidative capacity and obesity. In order to address the potential influence of sex on drug effects,^{14,15} both males and females were studied.

Methods

Model of Metabolic Syndrome

All experimental procedures were approved by the University of Michigan Committee for the Care and Use of Animals and were in accordance with the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals. We studied five male and five female rats of both HCR and LCR type (total $n = 20$) from the 26th generation, with ages between 10–12 months. The rats were maintained on a 12-hour light: 12 hour dark cycle (lights on at 6:00 AM) and *ad libitum* food and water were provided.

The development of these rat models using artificial selection and the maintenance of the rat colonies has been described in detail elsewhere.⁹ Briefly, the rats were tested for endurance running capacity on a treadmill. The treadmill was operated at a constant slope of 15 degrees with a speed of 10m/min. The rat was run to exhaustion while the speed was being increased at the rate of 1m/min every 2 min. The failure to keep pace with the treadmill resulted in the rats receiving a mild shock (1.2 mA, 3Hz) from a metal grid placed at the base of the treadmill. The failure to keep pace with the treadmill on three consecutive runs was determined as exhaustion. The test was repeated on five consecutive days.

The details of the individual body weights, best distance run, and the best time over a set of five trials for the animals in this study is provided in Table 2. It should be noted that the capacity of HCRs to run longer a distance in less time is an inherent trait and is not a result of training exercise. Similarly, the LCR rats are inherently characterized by obesity and run significantly shorter distances as compared to HCRs. The mean body weight of male LCR rats ($606.4\text{g} \pm 37.38$; 95% CI: 560.0–652.8) was significantly higher than the mean body weight of the male HCR rats ($371.0\text{g} \pm 21.30$; 95% CI: 344.6–397.4) ($p = 0.004$). Similarly, the mean body weight of female LCR rats ($302.6\text{g} \pm 8.14$; 95% CI: 292.5–312.7) was significantly higher than the mean body weight of the female HCR rats ($231.0\text{g} \pm 7.38$; 95% CI: 221.8–240.2) ($p = 0.004$). The mean body weight of the male LCR and HCR rats was also significantly higher than the mean body weight of the female LCR ($p = 0.004$) and female HCR rats ($p = 0.004$), respectively.

Determination of MAC

All rats were used for isoflurane and sevoflurane experiments with an interval of at least 3–4 weeks between anesthetic exposures. The requirements for both the anesthetics were measured as MAC using a bracketing design.¹⁶ MAC was chosen as the primary dependent variable of interest because other measures such as time to induction could be subject to pharmacokinetic influence via higher BMI or cardiovascular differences, as opposed to the steady-state design of MAC at equilibrium.¹⁶ A week before the experiment, each rat was habituated to a clear-walled anesthesia induction chamber (10.0 inches $\times$ 4.7 inches $\times$ 4.0

inches) on 3 separate days for 15 min each day. The habituation as well as the experimental procedure were conducted between 8:30 AM-12:00 PM in order to control for circadian influences. Anesthetic induction was achieved with isoflurane (2.5%) and sevoflurane (4.5%) delivered in 100% oxygen at a flow rate of 0.5 L/min. After the loss of righting reflex as a surrogate for loss of consciousness, the animal was positioned on an inclined polycarbonate platform in dorsal recumbency for endotracheal intubation (Small Animal Intubation Kit, Kent Scientific, Torrington, CT). A 16G catheter (Exel Safelet Cath, Exelint International Co., Los Angeles, CA) modified to have a thick sleeve/cuff on the upper one-third of the tubing, which allowed a sealed connection with the trachea, was used. Thereafter, the rat was connected to a nonbreathing gas circuit and the lungs artificially ventilated under constant pressure mode (TOPO Dual Mode Ventilator, Kent Scientific, Torrington, CT). Inspiration pressure was maintained between 10–15 cmH₂O and respiration rate was adjusted to maintain end-tidal CO₂ between 30–45 mmHg. The end-tidal CO₂ and the anesthetic concentration were monitored using an inline Datex Capnomac Ultima analyzer (Datex Medical Instrumentation, Inc., Tewksbury, MA). Rectal temperature was monitored and maintained at 37 ± 1 degrees Celsius using a heat lamp and water-based heating system (TP-500 Heat therapy Pump, Gaymar Industries Inc., Orchard park, NY). The heart rate and oxygen saturation were continuously monitored using a MouseOx monitor (Starr Life Sciences, Corp., Oakmont, PA). The animal was equilibrated to either isoflurane (1.7%) or sevoflurane (2.7%) for 30 minutes, after which a noxious mechanical stimulus was applied until a gross purposeful movement (positive response) occurred within 60 seconds. Purposeful movement was defined as what appeared to be voluntary movement of the limbs or movement related to change of body posture (positive response), as opposed to the movement of the whiskers, or slight muscular twitching (negative response). The stimulus consisted of a clamp to the upper third of the tail using a 10-inch hemostat (Roboz RS-7182), with the point of contact at the tip of the hemostat and with the hemostat closed to the first ratchet. During the application of the stimulus, the hemostat was oscillated at 45 degrees at 1 Hz. If there was no response after the application of stimulus for 60 s, the anesthesia was decreased by 10%. If a positive response occurred within 60 s then the anesthesia was increased by 10%. The increment or decrement of anesthetic was followed by equilibration for 30 minutes after which another identical stimulus was applied. Each subsequent stimulus was provided at a site proximal to the first test site. The determination of the positive or negative response was based on the concurrence of two experimenters. The MAC was calculated to be an average of i) the maximum anesthetic concentration that evoked a positive response to the noxious stimulus and ii) the minimum anesthetic concentration that prevented a positive response to the noxious stimulus. A pilot study to validate the MAC procedure was performed in male Sprague-Dawley rats. The pilot data on the MAC for isoflurane (1.47% ± 0.24 - average of two) and sevoflurane (2.1%) were consistent with the MAC reported in the literature for isoflurane (1.51% ± 0.12)¹⁷ and sevoflurane (2.4% ± 0.30)¹⁸ (Table 3).

Statistical Analyses

The statistical tests were performed using the software package Graph Pad Prism 5.01 (La Jolla, CA). The MAC data for isoflurane and sevoflurane from the combined pool of LCR and HCR rats were confirmed to be normally distributed (D'Agostino and Pearson test) and were compared using a two-tailed unpaired t-test. A nonparametric test (two-tailed Mann-Whitney) was used to compare the MAC for male and female groups within and between each phenotype. A one-tailed Mann-Whitney test was used to compare the body weight of the male and female rats within and between each phenotype. The data are reported as mean ± standard deviation (SD) along with the 95% confidence interval (CI). A p-value of <0.05 was considered statistically significant.

Results

The MAC for isoflurane and sevoflurane for individual LCR and HCR rats of either sex are shown in Table 2. The mean isoflurane-MAC for the HCR rats ($1.90\% \pm 0.19$; 95% CI: 1.76–2.03) was significantly higher as compared to the mean isoflurane-MAC for LCR rats ($1.52\% \pm 0.13$; 95% CI: 1.42–1.62) ($p = 0.0001$, $t = 5.019$, $df = 18$) (Table 3; Fig. 1A). Further analysis comparing the MAC between male and female rats of LCR and HCR type showed that the mean isoflurane-MAC for the male HCR rats ($1.92\% \pm 0.1$; 95% CI: 1.78–2.05) was significantly higher as compared to the mean isoflurane-MAC for male LCR rats ($1.48\% \pm 0.1$; 95% CI: 1.34–1.61) ($p = 0.01$) and female LCR rats ($1.56\% \pm 0.16$; 95% CI: 1.35–1.76) ($p = 0.01$) (Fig. 1B). Furthermore, the mean isoflurane-MAC for the female HCR rats ($1.88\% \pm 0.26$; 95% CI: 1.54–2.21) was also significantly higher as compared to the mean isoflurane-MAC for male LCR rats ($1.48\% \pm 0.1$; 95% CI: 1.34–1.61) ($p = 0.02$) (Fig. 1B). The isoflurane-MAC was not significantly different between the male and female rats within each phenotypic group (Fig. 1B).

In contrast to isoflurane, the MAC for sevoflurane was not significantly different between the HCR ($2.76\% \pm 0.27$; 95% CI: 2.56–2.96) and LCR rats ($2.53\% \pm 0.38$; 95% CI: 2.25–2.80) ($p = 0.13$, $t = 1.57$, $df = 18$) (Table 3; Fig. 2A). The comparison of sevoflurane-MAC for male and female rats of both LCR and HCR type showed that none of the groups differed significantly from each other ($p = 0.13$) (Fig. 2B).

Discussion

The results show for the first time that the mean isoflurane-MAC ($1.52\% \pm 0.13$) in LCR rats, which display obesity and symptoms related to human metabolic syndrome, were similar to the published MAC for isoflurane in normal rats ($1.51\% \pm 0.12$).¹⁷ Isoflurane has been shown to have a long time constant for equilibration with fat, which exceeds the typical duration of anesthetic delivery.¹⁹ The blood perfusion of fat tissue decreases with increasing adiposity.²⁰ Therefore, considered together, it is apparent that the effect of increased adiposity on isoflurane requirements would be minimal. Interestingly, the mean isoflurane-MAC for HCR rats ($1.90\% \pm 0.19$) was significantly higher as compared to the isoflurane-MAC for LCR rats ($1.52\% \pm 0.13$) and was elevated to a similar extent (about 20% increase) as compared to the isoflurane-MAC published for normal rats ($1.51\% \pm 0.12$)¹⁷ (Fig. 1 and Table 3). The mean sevoflurane MAC was not significantly different between male and female LCR and HCR rats. A further validation of the lack of a significant difference in the mean sevoflurane-MAC between LCR and HCR rats is provided by a recent study in human subjects which showed that the presence of obesity does not prolong the induction or emergence from sevoflurane anesthesia.²¹

It is possible that the present difference in the isoflurane-MAC between LCR and HCR rats could be a result of differential tolerance to the mechanical noxious stimulus used in this study. However, a previous study found no significant difference in the mechano-sensory responses between LCR and HCR rats as quantitatively assessed through von Frey testing.²² The present results encourage future MAC studies using additional sensory modalities.

Naturally occurring genotypic differences affect MAC.²³ Furthermore, genetic manipulations affecting ion channels have been shown to alter anesthetic sensitivity.^{24,25} Recently, Chae et al.²⁶ reported a differential effect of inactivation of TRESK (two pore potassium channel) gene on anesthetic sensitivity. The knockout mice lacking TRESK showed decreased sensitivity and hence increased MAC for isoflurane.²⁶ However, TRESK inactivation did not affect the sensitivity to sevoflurane, halothane and desflurane.²⁶ Collectively, the present results along with the published literature support a genetic basis

for differences in anesthetic sensitivity that is agent-specific. Future studies involving genetic manipulations of ion channels in LCR and HCR rats may provide further support to an underlying genetic basis for the differential anesthetic sensitivity between LCR and HCR rats. Neither LCR nor HCR rats showed any sex-specific differences in the MAC for either isoflurane or sevoflurane. This is in agreement with a previous report that the genotype rather than sex of the subject is a major determinant of anesthetic sensitivity.²³

The current study has a number of limitations. First, caution is warranted when applying interpretations of animal data to clinical care in humans. Second, we did not test all clinically relevant anesthetics; future studies might include drugs such as desflurane. Third, a larger number of animals in the sevoflurane group might have resulted in a significant difference in the MAC of HCR and LCR rats. However, even assuming such significance, the effect size and thus the clinical relevance would likely be minimal. This is also true for conclusions regarding anesthetic sensitivity across males and females.

In conclusion, obesity and associated co-morbidities did not affect inhaled anesthetic requirements of isoflurane and sevoflurane, as measured by MAC. These novel results support human observational data suggesting that obesity is not a risk factor for intraoperative awareness.³ Additionally, these data support the view that future anesthesia-related studies of metabolic syndrome in rats will not be confounded by extreme alterations in MAC. HCR rats displayed increased anesthetic requirements for isoflurane; both anesthetic requirements and aerobic fitness are complex, polygenic traits. The differential effects of HCR on isoflurane and sevoflurane support a genetic and drug-specific basis for anesthetic sensitivity. The present finding of strain-specific effects are consistent with studies documenting significant differences between HCR and LCR rats in the response to acute²⁷ and chronic²² nociceptive input. Considered together, these data support the interpretation that this rodent model of metabolic syndrome¹² provides a unique resource for phenotyping the mechanisms by which obesity and metabolic syndrome impact anesthesia.

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Figure 1.

Minimum alveolar concentration (MAC) for isoflurane for A) the combined pool of male and female rats of LCR and HCR type, and B) the male and female rats of LCR and HCR type grouped separately. LCR – low aerobic capacity runners, HCR – High aerobic capacity runners. ***p < 0.001 as compared to the combined pool of male and female rats of LCR type, #p < 0.05 as compared to male LCR rats, §p < 0.05 as compared to female LCR rats

Figure 2. Minimum alveolar concentration (MAC) for sevoflurane for A) the combined pool of male and female rats of LCR and HCR type, and B) the male and female rats of LCR and HCR type grouped separately. LCR – low aerobic capacity runners, HCR – High aerobic capacity runners.

Table 1

Comparison of metabolic profile of LCR, HCR and human subjects

	LCR ¹²	HCR ¹²	Human Metabolic Syndrome
Visceral adiposity/body weight (%)	1.55 ± 0.39*	0.95 ± 0.32	Central/visceral obesity
Triglycerides (mg/dl)	67 ± 24*	25 ± 4	Raised (≥150 mg/dl)
Free fatty acids (meq/l)	0.64 ± 0.22*	0.33 ± 0.04	Raised
Fasting glucose (mg/dl)	110 ± 9*	92 ± 5	Raised (≥100 mg/dl)
Insulin (pM)	684 ± 195*	296 ± 172	Insulin resistance
Mean arterial blood pressure-24h (mmHg)	102 ± 6*	90 ± 7	Raised (SBP≥130, DBP≥85)

Data are reported as mean ± standard deviation.

* significant difference as compared to HCR.

Superscript number denotes citation from which the data are derived.

LCR – low aerobic capacity rats, HCR – high aerobic capacity rats, SBP – systolic blood pressure, DBP – diastolic blood pressure

Table 2

Individual characteristics and minimum alveolar concentration (MAC) for isoflurane (ISO) and sevoflurane (SEVO) for each low aerobic capacity and high aerobic capacity rat used in this study

Low Aerobic Capacity Rats						High Aerobic Capacity Rats					
Sex	Body wt (g)	Distance (meter)	Time (min)	ISO-MAC (%)	SEVO-MAC (%)	Sex	Body wt (g)	Distance (meter)	Time (min)	ISO-MAC (%)	SEVO-MAC (%)
Male	560	165.6	13.0	1.40	2.30	Male	365	2100.2	74.6	1.80	3.15
Male	605	192.5	14.6	1.40	2.55	Male	400	2048.5	73.5	2.00	2.85
Male	620	197.3	14.9	1.40	1.90	Male	341	1985.4	72.1	2.00	2.55
Male	587	197.6	14.9	1.60	2.55	Male	377	1919.3	70.7	1.80	2.85
Male	660	275.3	19.3	1.60	3.15	Male	372	1914.8	70.6	2.00	3.15
Female	294	245.7	17.7	1.60	2.55	Female	230	2402.2	80.9	2.20	2.55
Female	315	261.8	18.5	1.40	2.55	Female	240	2227.7	77.3	2.00	2.85
Female	305	341.6	22.6	1.80	2.30	Female	223	2175.6	76.2	2.00	2.85
Female	297	403.7	25.5	1.40	2.30	Female	237	1626.4	63.9	1.60	2.30
Female	302	409.1	25.7	1.60	3.15	Female	225	1613.8	63.6	1.60	2.55

Table 3

Minimum alveolar concentration (MAC) for isoflurane and sevoflurane for normal, LCR and HCR rats

MAC	Normal	LCR	HCR
Isoflurane (%)	1.51 ± 0.12 ¹⁷	1.52 ± 0.13	1.90 ± 0.19
Sevoflurane (%)	2.40 ± 0.30 ¹⁸	2.53 ± 0.38	2.76 ± 0.27

Data are reported as mean ± standard deviation. Normal – normal Sprague Dawley/Wistar rats as used in the cited references; LCR – low aerobic capacity rats; HCR – high aerobic capacity rats. Superscript numbers refer to citations from which data are derived.