



## Effect of Obesity on Awakening Time after Isoflurane/Sevoflurane Inhalation Anesthesia in Dogs

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### ABSTRACT

To elucidate the relationship between obesity, awakening time, and anesthesia in dogs, we conducted a comparative analysis of the awakening time following isoflurane and sevoflurane anesthesia in both standard-weight and obese groups. Six female beagle dogs within the standard weight range underwent 1-hour inhalation anesthesia with either isoflurane or sevoflurane. We recorded the time of extubation, head lift, and standing. Additionally, a parallel experiment was conducted on the same test animals after inducing obesity through nutritional management, with criteria for obesity defined as a body conditioning score of 4 or higher and a body fat percentage of 30% or higher. Under isoflurane anesthesia, we observed a tendency for a longer awakening time in the obese group compared to the standard weight group. However, this trend was not evident with sevoflurane anesthesia. Furthermore, when comparing awakening time with both anesthetics, no significant difference was found between the standard weight groups. In contrast, within the obese group, awakening time was significantly prolonged with isoflurane anesthesia compared to sevoflurane anesthesia. These results confirm that obesity contributes to delay awakening in dogs. Additionally, in the anesthesia management of obese dogs, the use of sevoflurane is anticipated to reduce awakening time compared to isoflurane.

**Keywords:** Awakening time, Dog, Isoflurane, Obese, Sevoflurane.

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### INTRODUCTION

Generally, obese animals are associated with an increased risk during anesthesia. This is believed to be due to abnormalities in respiratory muscle function, thoracic compliance, and intra-abdominal pressure. Lung function is affected by body position, and in the supine position, ventilation volume decreases due to pressure on the diaphragm by intra-abdominal organs (Pelosi *et al.*, 1996; Casati and Putzu, 2005; Love and Cline, 2015). Additionally, elevated blood cholesterol levels in obese animals may lead to endocrine diseases such as diabetes and liver damage (Laflamme, 2006), potentially interfering with anesthetic metabolism. Furthermore, anesthetics are temporarily absorbed into adipose tissue, reducing their effectiveness and requiring larger amounts of anesthetics, making it challenging to emerge from anesthesia and placing strain on the body (Adams and Murphy, 2000; Eger and Saidman, 2005; Stoelting and Miller, 2007). Even if spontaneous breathing is observed during the postoperative awakening process, sufficient ventilation may not be ensured, leading to

hypoventilation, reduced excretion of inhaled anesthetics through exhalation, and delayed awakening (Pelosi *et al.*, 1996).

The choice of anesthetic is a critical factor influencing wakefulness. Isoflurane is commonly used as an anesthetic in dogs due to its lower solubility in blood and fat compared to previously used halothane. Isoflurane allows for rapid induction of anesthesia and has a low metabolic rate, thereby reducing the risk of postoperative liver damage caused by anesthetics (Eger, 2004; Steffey *et al.*, 2015). Conversely, sevoflurane, a recently prominent anesthetic, has a very low blood/gas partition coefficient of 0.63 (Sakai, 2005; Steffey *et al.*, 2015). It is a volatile anesthetic known for causing rapid induction and awakening. Sevoflurane also exhibits lower airway irritation than other anesthetics, enabling smooth induction and rapid awakening (Patel and Goa, 1996; Eger, 2004; Steffey *et al.*, 2015).

Agoliati *et al.*, (2000) conducted a meta-analysis of isoflurane and sevoflurane extubation times in humans, reporting a 13% reduction in mean

extubation time with sevoflurane compared to isoflurane. **Robinson et al. (1999)** similarly found that sevoflurane significantly reduced wakefulness time compared to isoflurane. However, **Behne et al. (1999)** reported no difference in wakefulness time between sevoflurane and isoflurane in young humans undergoing urinary surgery. While previous studies have investigated wake time differences between isoflurane and sevoflurane in obese and normal weight groups (**Lemmens et al., 2008**), such studies in dogs remain unknown.

Therefore, we compared the awakening time of standard-weight dogs and obese dogs under isoflurane and sevoflurane anesthesia, investigating the influence of obesity on awakening time.

## MATERIALS AND METHODS

### Animals

The test animals used were six clinically healthy female beagle dogs. This was defined as the standard weight group (weight 8.3–10.2 kg, BCS 3, body fat percentage 15–24%). BCS was assessed by a validated 5-point scale (**Toll et al., 2010**). The test dogs were fed once a day and were given free access to water. During the experiment, all animals were fasted for 12 hours before being used for the experiment. After the experiment for the standard weight group, the feeding method of the test animals was changed to twice a day. When the BCS exceeded 4 and the body fat percentage exceeded 30%, they were subjected to the experiment again as an obese group (weight 10.0–15.0 kg).

When body fat percentage and BCS were measured in the standard weight group and the obese group, the body fat percentage was 15–24% (average 16%) and BCS was 3 in the standard weight group. In the obese group, body fat percentage was 31–42% (average 35%), and BCS was 4 or higher. The body fat percentage was measured using a Health Lab Canine Body Fat Metre (Kao Corporation, Tokyo, Japan). The hair on the dog's back was shaved, disinfectant ethanol was applied, and the electrodes were applied directly to the skin three times. The average value was recorded. The animal experimentation protocol was approved by the Institutional Animal Care and Use Committee of Kitasato University (Approval No. 10-080).

### Experimental method

A 22G indwelling needle was placed in the cephalic vein of the test animals. Atropine sulfate (Mitsubishi Tanabe Pharma, Osaka, Japan) 0.025 mg/kg and butorphanol tartrate (Stadol<sup>®</sup>, Bristol-Myers Tokyo, Japan) 0.1 mg/kg were administered intravenously as premedication. To induce anesthesia, 6 mg/kg of propofol (Rapinovel<sup>®</sup>, Intervet, Tokyo, Japan) was administered (**Devito et al., 2020**), and

tracheal intubation was performed. In addition, to maintain anesthesia, the dose was adjusted to isoflurane 1.5 MAC (2.0%) (Isoflu<sup>®</sup>, Sumitomo Dainippon Pharma, Osaka, Japan) or sevoflurane 1.5 MAC (3.5%) (Sevoflu<sup>®</sup>, Maruishi Pharmaceutical, Tokyo, Japan) and maintained by inhalation (**Steffey et al., 2015**). Ventilation conditions were adjusted to a tidal volume of 15 ml/kg and a ventilation frequency of 10 times/min. After intubation, lactated Ringer's solution was infused at 5 ml/kg until the end of anesthesia. The anesthesia time was 1 hour, and the extubation time, head lift time, and standing time were measured after the end of anesthesia. Extubation was determined when sufficient spontaneous breathing was achieved and oral paralysis had disappeared, and the time of extubation after the swallowing reflex was observed was recorded. Head lift was recorded as the time the subjects were able to lift their heads on their own for 5 seconds or more without assistance. The time the participants were able to stand on their own for more than 5 minutes was recorded.

### Data analysis

The results were expressed as mean value  $\pm$  standard deviation. For statistical analysis, a paired t-test was performed on the wakefulness time values of the standard weight group and the obese group, as well as isoflurane and sevoflurane, and a significant difference was determined at  $P < 0.05$ .

## RESULTS

When maintained with isoflurane, there was no significant difference in extubation and onset time of head lift and standing in the obese group compared with the standard weight group, but there was a tendency for it to be longer (**Fig.1**).

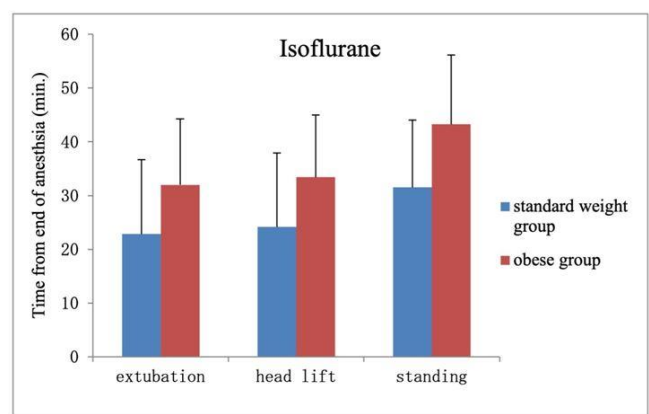


Fig.1: Comparison of awakening time between standard weight and obese groups in isoflurane anesthesia.

When maintained with sevoflurane, no significant differences were observed in the onset times of extubation, head lift, and standing between the standard weight group and the obese group (**Fig.2**).

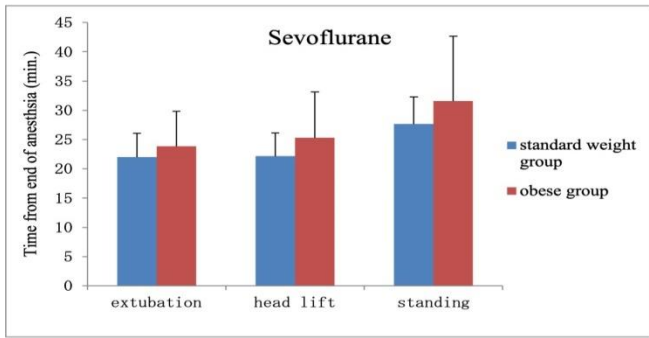


Fig.2: Comparison of awakening time between standard weight and obese groups in sevoflurane anesthesia.

When comparing the **awakening** time of isoflurane and sevoflurane in the standard weight group and the obese group, no significant difference was observed between isoflurane and sevoflurane in the standard weight group (Fig.3).

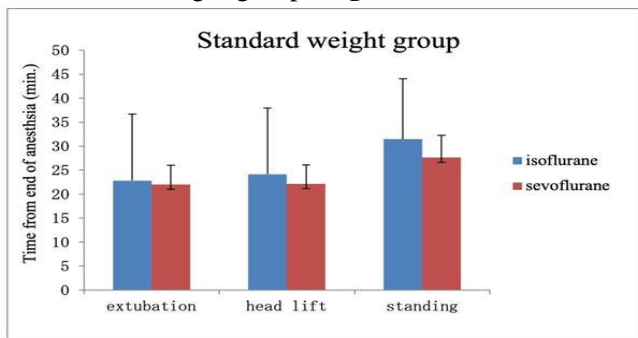


Fig.3: Comparison of awakening time between isoflurane and sevoflurane in the standard weight group.

In the obese group, the onset time of extubation and head lift tended to be longer with isoflurane than with sevoflurane, and the onset time of standing was significantly prolonged ( $P < 0.05$ , Fig.4).

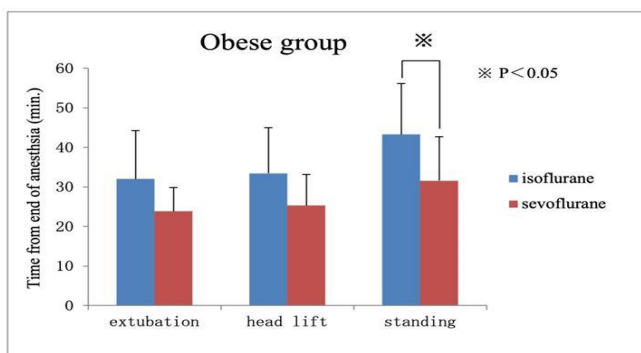


Fig. 4: Comparison of awakening time between isoflurane and sevoflurane in the obese group.

## DISCUSSION

It is commonly acknowledged that obese animals face an increased risk during anesthesia. These risks include the potential for drug overdosing due to

excess fat tissue, the prevalence of underlying diseases such as cardiovascular and liver issues (Laflamme, 2006; Love and Cline, 2015; Tropf *et al.*, 2017), and the application of fat-soluble anesthetics to body fat, where they may be stored (Stoelting and Miller, 2007). Adipose tissue and skeletal muscle, comprising approximately 70% of body tissue, receive less than 25% of cardiac output blood flow, leading to the gradual uptake of anesthetics over several hours and providing pharmacologically inert storage akin to a tank (Adams *et al.*, 2000; Stoelting and Miller, 2007). Moreover, it is suggested that when drug plasma concentration decreases after anesthesia, fat-soluble drugs stored in adipose tissue are released into circulation, causing delayed awakening (Stoelting and Miller, 2007). This delayed awakening not only stresses the animal's body but also results in potential economic costs, such as the effort of the operator who must remain with the animal until it awakens. Hence, rapid awakening proves beneficial for both the patient and the surgeon.

When maintained with isoflurane, there was a tendency for the onset time of extubation, head lift, and standing to be longer in the obese group compared to the standard weight group. Isoflurane, currently the most widely used drug, boasts numerous advantages, including high stability, a small blood gas partition coefficient of 1.4, rapid induction and awakening, non-irritation to the heart, and non-flammability (Steffey *et al.*, 2015). However, isoflurane induces respiratory depression, reducing tidal volume during anesthesia (Groeben *et al.*, 2004). Additionally, in obese animals, excess adipose tissue compresses the thorax and abdomen, leading to decreased expiratory reserve, vital capacity, and functional residual capacity. This increased weight impairs diaphragm movement, further reducing ventilation (Pelosi *et al.*, 1996; Casati and Putzu, 2005; Stoelting and Miller, 2007). Decreased ventilation results in reduced exhaled anesthetic excretion during awakening, increasing the likelihood of delayed awakening (Adams and Murphy, 2000). Furthermore, the accumulation of fat-soluble anesthetics in adipose tissue is considered a cause of delayed awakening. Nonetheless, some human studies have not supported the notion that volatile anesthetics stored in adipose tissue delay the emergence of anesthesia in obese patients (Lebuffe *et al.*, 2010). Therefore, the observed tendency for longer wakefulness in the obese group with isoflurane may be attributed to decreased anesthetic excretion due to decreased alveolar ventilation rather than drug redistribution accumulated in adipose tissue.

Conversely, when maintenance was performed with sevoflurane, no significant difference was observed in wakefulness time between the two groups.



Sevoflurane is nonflammable, possesses a very low blood/gas partition coefficient of 0.68, and induces and awakens extremely quickly. The metabolic rate in the body is as low as 2.89%, causing minimal damage to the liver or kidneys. Additionally, it has a less irritating odour and is highly adjustable (Patel and Goa, 1996). Adipose tissue is said to receive only approximately 5% of cardiac output (Stoelting and Miller, 2007), and sevoflurane's very low blood/gas partition coefficient implies that obesity may not significantly impact wakefulness. Moreover, the fact that sevoflurane induces less respiratory depression than isoflurane (Groeben *et al.*, 2004) might explain the absence of wakefulness prolongation.

Comparing the awakening times of isoflurane and sevoflurane in the standard weight group and the obese group, there was no significant difference in the awakening time between the two anesthetics in the standard weight group. However, the obese group exhibited significantly lower awakening times for extubation, head elevation, and standing up. There was a tendency for the onset time to be shorter with sevoflurane than with isoflurane, particularly with a significant shortening observed in standing time. Human studies have also reported that sevoflurane shortens wakefulness time in obese patients (Lemmens *et al.*, 2008; Lebuffe *et al.*, 2010). In obese dogs with poor ventilation, sevoflurane anesthesia shortens wakefulness time more than isoflurane. This suggests promising outcomes to anticipate.

A limitation of this study is the use of healthy beagle dogs, where factors affecting recovery from anesthesia, such as those in the circulatory and endocrine systems, may differ from clinical cases. Therefore, further research using clinical cases is necessary.

## CONCLUSION

Obesity has been identified as a cause of delayed awakening in dogs. Additionally, in the anesthesia management of obese dogs, the use of sevoflurane anesthesia is expected to reduce awakening time more effectively than isoflurane.

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## Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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