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Volatile anesthetics maintain tidal volume and minute ventilation to a greater degree than propofol under spontaneous respiration

Xuechao Hao^{1,2}, Mengchan Ou^{1,2}, Yu Li^{1*} and Cheng Zhou^{1,2*}

Abstract

Background: Although general anesthetics depress spontaneous respiration, the comprehensive effect of general anesthetics on respiratory function remains unclear. We aimed to investigate the effects of general anesthetics on spontaneous respiration in non-intubated mice with different types and doses of general anesthetic.

Methods: Adult C57BL/6 J mice were administered intravenous anesthetics, including propofol and etomidate, and inhalational anesthetics, including sevoflurane and isoflurane in vivo at doses of 0.5-, 1.0-, and 2.0-times the minimum alveolar concentration (MAC)/median effective dose (ED₅₀) to induce loss of the righting reflex (LORR). Whole-body plethysmography (WBP) was applied to measure parameters of respiration under unrestricted conditions without endotracheal intubation. The alteration in respiratory sensitivity to carbon dioxide (CO₂) under general anesthesia was also determined. The following respiratory parameters were continuously recorded during anesthesia or CO₂ exposure: respiratory frequency (FR), tidal volume (TV), minute ventilation (MV), expiratory time (TE), inspiratory time (TI), and inspiratory–expiratory time ratio (I/E), and peak inspiratory flow.

Results: Sub-anesthetic concentrations (0.5 MAC) of sevoflurane or isoflurane increased FR, TV, and MV. With isoflurane and sevoflurane exposure, the CO₂-evoked increases in FR, TV, and MV were decreased. Compared with inhalational anesthetics, propofol and etomidate induced respiratory suppression, affecting FR, TV, and MV. In 100% oxygen (O₂), FR in the group that received propofol 1.0-times the ED₅₀ was 69.63 ± 33.44 breaths/min compared with 155.68 ± 64.42 breaths/min in the etomidate-treated group. In the same groups, FR was 88.72 ± 34.51 breaths/min and 225.10 ± 59.82 breaths/min, respectively, in 3% CO₂ and 144.17 ± 63.25 breaths/min and 197.70 ± 41.93 breaths/min, respectively, in 5% CO₂. A higher CO₂ sensitivity was found in etomidate-treated mice compared with propofol-treated mice. In addition, propofol induced a greater decrease in FR, MV, and I/E ratio compared with etomidate, sevoflurane, and isoflurane at equivalent doses (all *P* < 0.05).

Conclusions: General anesthetics differentially modulate spontaneous breathing in vivo. Volatile anesthetics increase FR, TV, and MV at sub-anesthetic concentrations, while they decrease FR at higher concentrations. Propofol consistently depressed respiratory parameters to a greater degree than etomidate.

Keywords: General Anesthetics, Spontaneous Respiration, Whole-body Plethysmograph

Background

More than 300 million major surgical procedures requiring general anesthesia or analgesics are conducted worldwide each year [1, 2]. General anesthetics and analgesics induce respiratory depression, which is a critical issue in clinical practice, especially for sedative procedures

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requiring maintenance of spontaneous respiration [3]. Multiple studies have explored the depressant effect of opioids on respiration, but the effects of general anesthetics are not well elucidated [4, 5].

General anesthetics exert various clinically important actions, including hypnosis, amnesia, and immobility [6], as well as respiratory disturbance. Even though a depressant effect is a commonly suggested effect of general anesthetics, significant differences are observed in respiratory behavior between general anesthetics. Propofol depresses ventilation by affecting central chemoreceptor sensitivity, reducing the ventilatory response to hypercapnia, and reducing the ventilatory adaptation to hypoxia, even at sub-anesthetic doses [7, 8]. During dexmedetomidine infusion, respiratory frequency (FR) is significantly increased, and the overall apnea/hypopnea index is significantly decreased [9].

Volatile anesthetics, including isoflurane and sevoflurane, are preferred over intravenous anesthetics, such as propofol and etomidate, in conditions necessitating maintenance of spontaneous respiration, such as anticipated difficulties with endotracheal intubation. Both volatile anesthetics and intravenous anesthetics decrease FR, tidal volume (TV), and minute ventilation (MV) [10–13]. However, early clinical studies with small sample sizes indicated that volatile anesthetics, including enflurane, isoflurane, and sevoflurane, increase FR [10, 14]. Multiple structures associated with respiration are affected by general anesthetics, including the ventral medulla, the retrotrapezoid nucleus (RTN), and phrenic motor neurons [13, 15]. Uncovering the respiratory-related response in vivo during exposure to general anesthetics may help to identify the underlying mechanism. However, limitations exist in previous studies, including restricted study doses and time courses.

As a physical stimulant, carbon dioxide (CO₂) plays an important role in modulation of respiration by general anesthetics. Studies revealed an increase in the partial pressure of CO₂ in artery (PaCO₂) after exposure to general anesthetics. The increase in FR under volatile anesthesia is considered to be a compensatory effect resulting from an elevated PaCO₂ and respiratory depression [10, 14, 16]. However, lack of an increase in FR was found during intravenous anesthesia. Differences in the manipulation of neuronal processes that are sensitive to CO₂ might contribute to the discrepancy in respiratory responses induced by volatile versus intravenous anesthetics. Even so, the effect of general anesthetics on respiratory responses to CO₂ remains unclear.

Inhaled and intravenous anesthesia are two most common approaches in clinic. In this study, we chose these four classic drugs of inhaled (sevoflurane and isoflurane) and intravenous anesthetics (propofol and

etomidate). The dose-related and time-related effects of the four general anesthetics on respiratory behaviors in mice were explored using whole-body plethysmography (WBP). The respiratory responses to CO₂ during exposure to general anesthetics were also explored. The results of this study may encourage further research into the mechanisms underlying modulation of respiration by general anesthetics.

Methods

Animals

All protocols were approved by the Institutional Animal Experimental Ethics Committee of Sichuan University (Chengdu, Sichuan, China) in accordance with the animal care guidelines of the National Institutes of Health. Endeavors were made to minimize suffering and to reduce the number of mice used.

Experiments were performed in wild type C57BL/6 J male mice aged 12 weeks, weighing 20–25 g. All mice were housed in standard conditions, with a 12-h light/dark cycle and with ad-libitum access to food and water. All experiments were performed during the light cycle (from 9:00 am to 5:00 pm).

Whole-body Plethysmograph

Whole-body Plethysmograph (Buxco FinePointe Series WBP 4-site system, Data Sciences International, New Brighton, MN, USA) offers a precise, non-invasive, quantitative approach to measure respiratory parameters in conscious, freely moving animals. The system relies on a specially designed chamber in which the subject is placed and allowed to breathe freely under natural conditions, unrestrained and untethered.

The volume of the plethysmography chamber was 480 ml. A constant flow was driven by an oxygen (O₂) cylinder connected to the chamber, which ensured continuous flow at 0.5 ± 0.1 L/min of gas, thereby preventing CO₂ accumulation. Hyperoxia and hypercapnia and/or volatile anesthetics were continuously induced/administered into the chamber through the flow pump.

FinePointe software was used to analyze incoming data and create instant reports. The following respiratory parameters were registered: FR, TV, MV, peak inspiratory flow, inspiratory time (Ti), and expiratory time (Te). Except for FR, all measured respiratory parameters (including TV and MV) were normalized to body weight to make them comparable between mice with different body weights. One technician who was blinded to the animal groups measured the respiratory outputs in vivo, and another researcher analyzed the data.

General anesthetics and CO₂ administration

Two volatile anesthetics (sevoflurane and isoflurane) and two intravenous anesthetics (propofol and etomidate) were used in this study. According to our previous studies and studies of others [17, 18], equipotent doses for inducing loss of the righting reflex (LORR) (minimum alveolar concentration [MAC]/median effective dose [ED₅₀]) of sevoflurane, isoflurane, propofol, and etomidate were 1.58%, 0.86%, 70 mg/kg (intraperitoneally [i.p.]), and 8.85 mg/kg (i.p.), respectively. We used doses of 0.5-, 1.0-, and 2.0-times MAC/ED₅₀ required to induce LORR. Propofol at doses of 70 mg/kg, and 140 mg/kg, and etomidate at doses of 8.85 mg/kg, and 17.7 mg/kg, were injected i.p., respectively. For inhalational anesthetics, different concentrations of sevoflurane (0.63%, 1.58%, and 3.16%) and isoflurane (0.34%, 0.86%, and 1.72%) were delivered. A sample size of 8–10 mice for each dose or concentration was used, and all mice were used only once.

Propofol and etomidate (Fresenius Kabi, Bad Homburg, Germany) were injected i.p. All mice received a similar injected volume to exclude the effects of volume variation on respiratory depression in the propofol and etomidate groups.

For sevoflurane (Abbott Pharmacology Ltd., Co., Shanghai, China) and isoflurane (North Chicago, IL, USA) administration, mice were kept in the plethysmography chamber, which comprised a gas inlet and outlet. Sevoflurane or isoflurane was applied into the chamber through the inlet, with a continuous flow of 100% O₂ at a rate of 0.5 ± 0.1 L/min. Concentrations of sevoflurane and isoflurane were monitored in real-time using the RGM monitor (Datex-Ohmeda, Louisville, CO, USA). For control mice, the chamber was filled with 100% O₂ at a flow rate of 0.5 L/min.

As indicated by our preliminary experiments, the concentration of sevoflurane or isoflurane in the chamber was balanced after 5 min of delivery, which was detected at the outlet. Drug washout was achieved by suctioning the chamber and flowing fresh air into the chamber between each experiment.

Behavior test

On the day of the experiment, mice were transported to the laboratory at least 2 h before the start of the experiment. Prior to recording, mice were placed into the plethysmography chamber with no restriction for a minimum of 2 h to allow acclimatization. Mice were awake and calm during testing. Over-excited mice with a high level of locomotor activity or environmental exploration were excluded from anesthetic treatment and behavioral testing.

For control mice, 100% O₂ was applied for 30 min. For mice exposed to anesthetic, different doses of sevoflurane, isoflurane, propofol, and etomidate (as mentioned above) were applied, respectively, with 100% O₂ for 30 min. Then, the hyperoxic–hypercapnic experiment was conducted with gas mixtures of 3% CO₂, 5% CO₂, and 7% CO₂ balanced with 100% O₂ (0.5 L/min). In the time-course experiments, mice were administered three anesthetics with 100% O₂ (1 L/min) for 30 min.

All experiments were performed at room temperature (22 °C ± 1.5 °C) and humidity (58% ± 5%). Calibration of the plethysmography chamber system was performed once per day before the experiment according to WBP instructions. After each recording, the chamber was cleaned thoroughly with 75% ethanol.

During the experiments, raw respiratory parameters were continuously recorded, and average values were calculated every 2 s. The behavioral state of mice was classified as immobile, exploring, grooming, or undefined. In practice, only data recorded during immobility was considered in the comparison, at least 15 min after propofol or volatile anesthetic delivery. Treatments and tests were conducted randomly on mice in different groups to preclude potential confounding factors. The behavioral test and respiratory parameter analysis were performed with independent researchers who were blinded to the study aims and protocol.

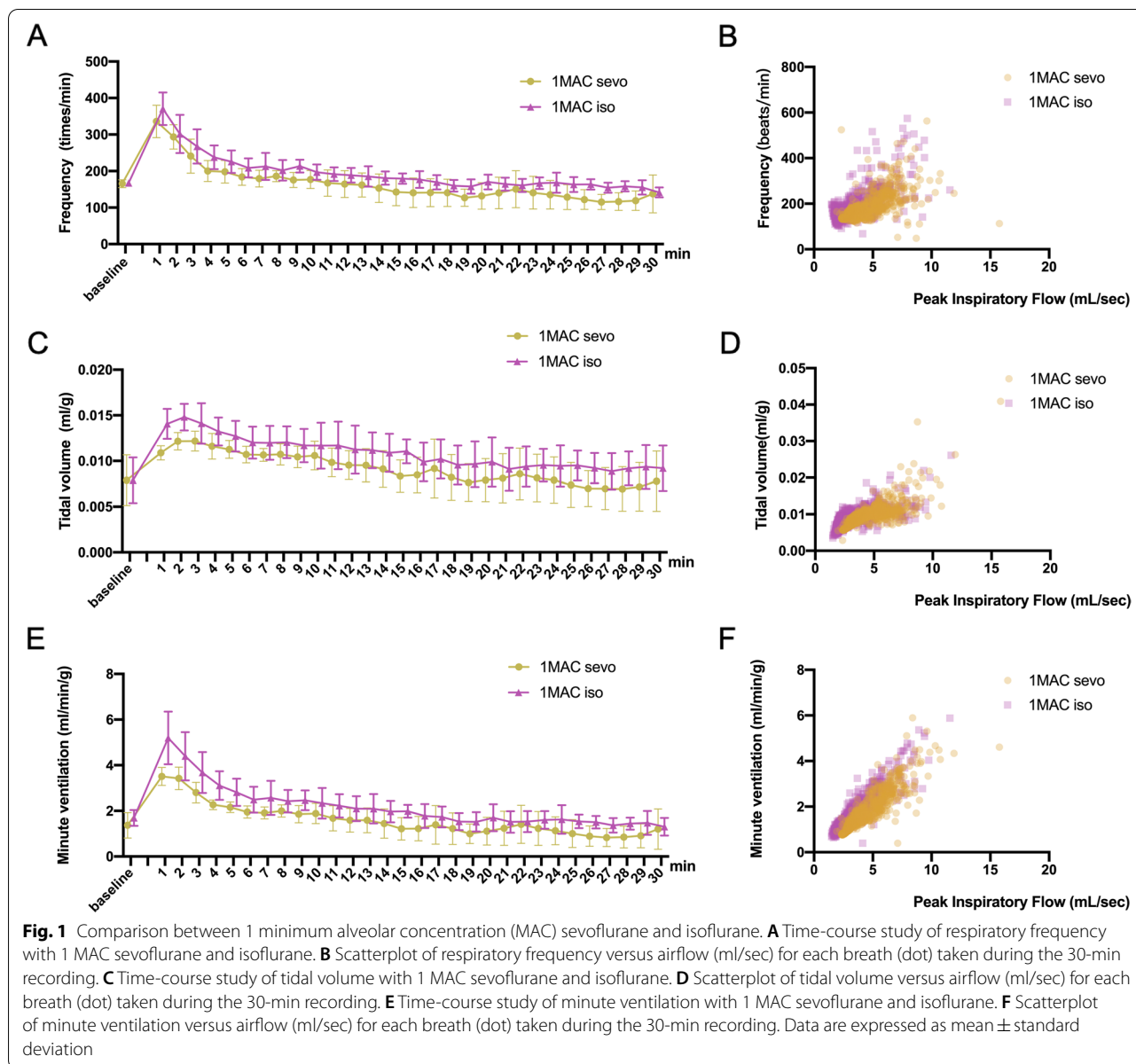
Statistical analysis

The distribution of values in each set of experiments was tested for normality using the D'Agostino-Pearson omnibus test or the Shapiro–Wilk test. Values are expressed as mean ± standard deviation. The means among groups were compared with with one -way or two-way analysis of variance followed by Bonferroni correction for post-hoc analysis. Differences among groups were considered statistically significant when *P* was < 0.05. Statistical analyses were performed using Prism 7.0 software (GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistics 22.0 (IBM Corp., NY, USA).

Results

Sub-anesthetic concentrations of volatile anesthetics increase FR, TV, and MV in wild type mice

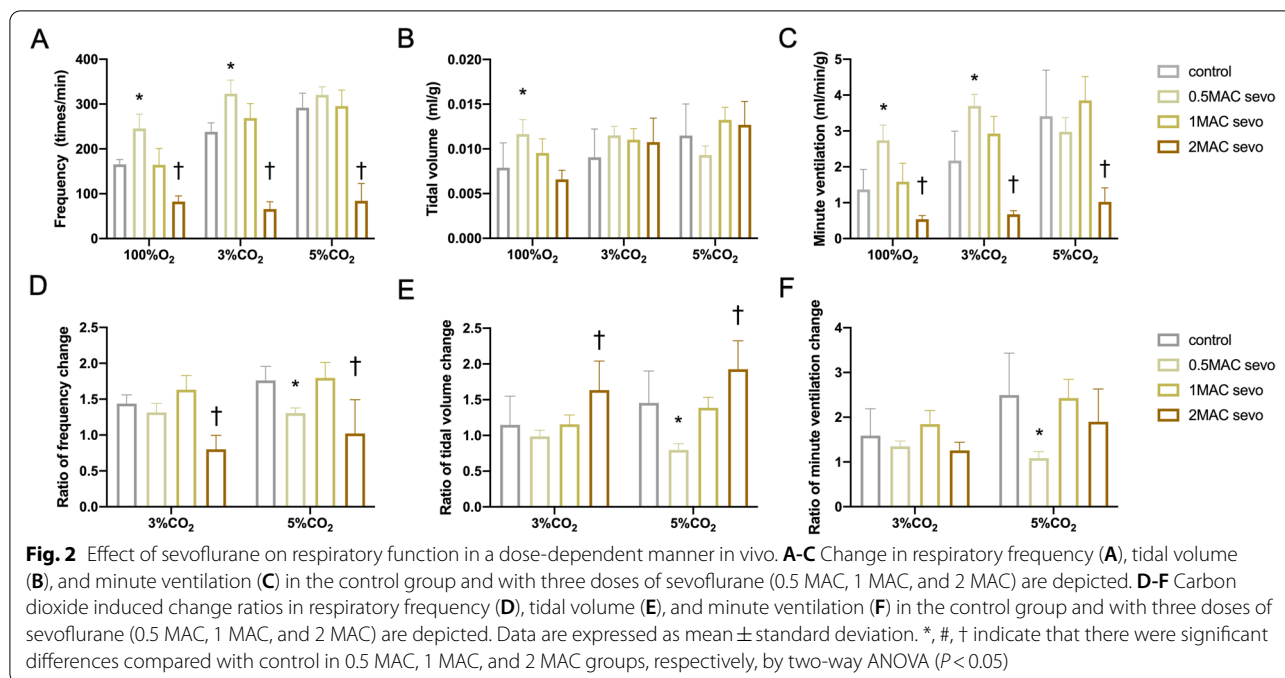
There were no measurable differences in respiratory activity among all experimental mice when exposed to room air, 100% O₂, 3% CO₂, and 5% CO₂ conditions (data not shown). During the comparison of inhalational anesthetics, mice had similar FR, TV, and MV values at baseline (100% O₂). Mice showed a reactive increase in FR, TV, and MV when exposed to 1 MAC sevoflurane and isoflurane with 100% O₂ at the beginning. Mice stabilized after 10–12 min of recording. The timeline with 1 MAC of sevoflurane and



isoflurane are presented in (Fig. 1 A-F). There was no difference between two groups in FR, TV and MV.

To compare if these two inhalational anesthetics affected breathing differently, we analyzed respiratory parameters during the period when mice were stable (at 10–12 min) during the 30-min recording. Both sevoflurane and isoflurane increased the respiratory output at concentrations of 0.5 MAC and 1 MAC (Fig. 2 A-F, Fig. 3 A-F). Specifically, at concentrations of 0.5 MAC, sevoflurane and isoflurane both increased FR from 165.57 ± 10.64 to 245.44 ± 31.88 breaths/min (Fig. 2 A, $P < 0.001$) and 174.29 ± 15.02 to 259.41 ± 37.62 breaths/min in 100% O₂, respectively (Fig. 3 A, $P < 0.001$). Similarly, mice exposed to 0.5 MAC

of sevoflurane and isoflurane exhibited increased ventilation under hypercapnia, as follows: sevoflurane: 3% CO₂ vs. 100% O₂ produced P values of 0.006, 0.950, and < 0.001 for FR, TV, and MV, respectively, and 5% CO₂ vs. 100% O₂ produced P values of 0.001, 0.027, and 0.403 for FR, TV, and MV, respectively; isoflurane: 3% CO₂ vs. 100% O₂ produced P values of < 0.001 , 0.431, and 0.001 for FR, TV, and MV, respectively, and 5% CO₂ vs. 100% O₂ produced P values of 0.004, < 0.001 , and < 0.001 for FR, TV, and MV, respectively. FR responses to increased CO₂ were all diminished with administration of 2 MAC sevoflurane (Fig. 2 D, $P < 0.001$ in both 3%CO₂ and 5%CO₂ conditions) and isoflurane (Fig. 3 D, $P < 0.001$ in both 3%CO₂



and 5%CO₂ conditions) but the TV responses were all increased in 2 MAC sevoflurane (Fig. 2 E, $P=0.003$ in 3%CO₂ and $P=0.004$ in 5%CO₂ conditions) and isoflurane (Fig. 3 E, $P < 0.001$ in both 3%CO₂ and 5%CO₂ conditions).

Propofol causes significant respiratory depression compared with etomidate

To explore the dose-dependent effect of intravenous anesthetics on respiratory depression, we used two different concentrations of propofol and etomidate (1 ED₅₀ and 2 ED₅₀, Fig. 4 A-D). We found that compared with 1 ED₅₀, propofol depressed TV in the group exposed to 2 ED₅₀ ($P=0.004$) (Fig. 4 Aii). Etomidate also depressed TV at a higher dose ($P < 0.001$) (Fig. 4 Cii). Scatter plot (tidal volume vs. airflow) also showed that compared to 1 ED₅₀, breathing in 2 ED₅₀ propofol group became slow and less forceful (Fig. 4 Bii).

In mice exposed to 1 ED₅₀ of propofol and etomidate, a time-course study revealed that propofol progressively reduced FR, TV, and MV and stabilized after 20 min during the 30-min exposure (Fig. 5 A, B, C). However, there was no further respiratory depression after respiration decreased to a relatively stable level (after 10 min) in the group that received 1 ED₅₀ etomidate (Fig. 5 A, B, C). Compared to propofol, etomidate causes less respiratory depression in FR (Fig. 5. D) and MV (Fig. 5 F). In addition, mice that received 1 ED₅₀ etomidate showed a diminished CO₂-dependent increase in FR, TV, and MV. However, mice that received 1 ED₅₀ propofol showed a significant increase

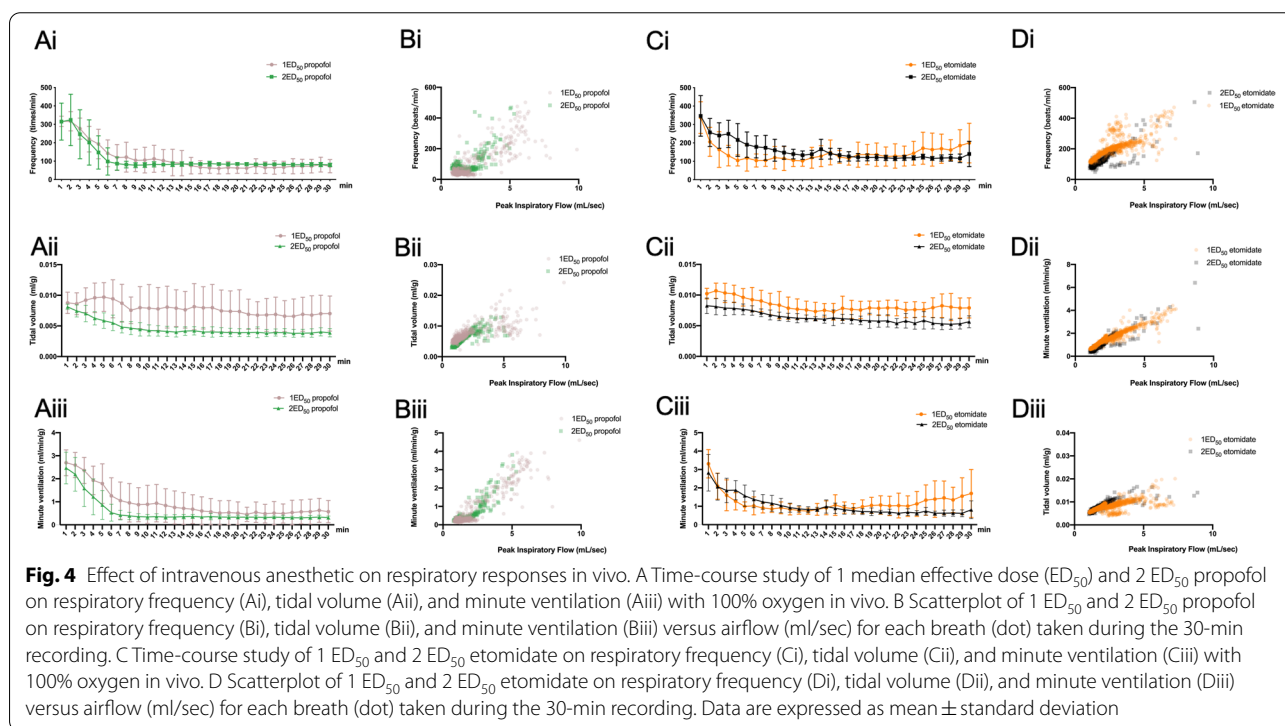
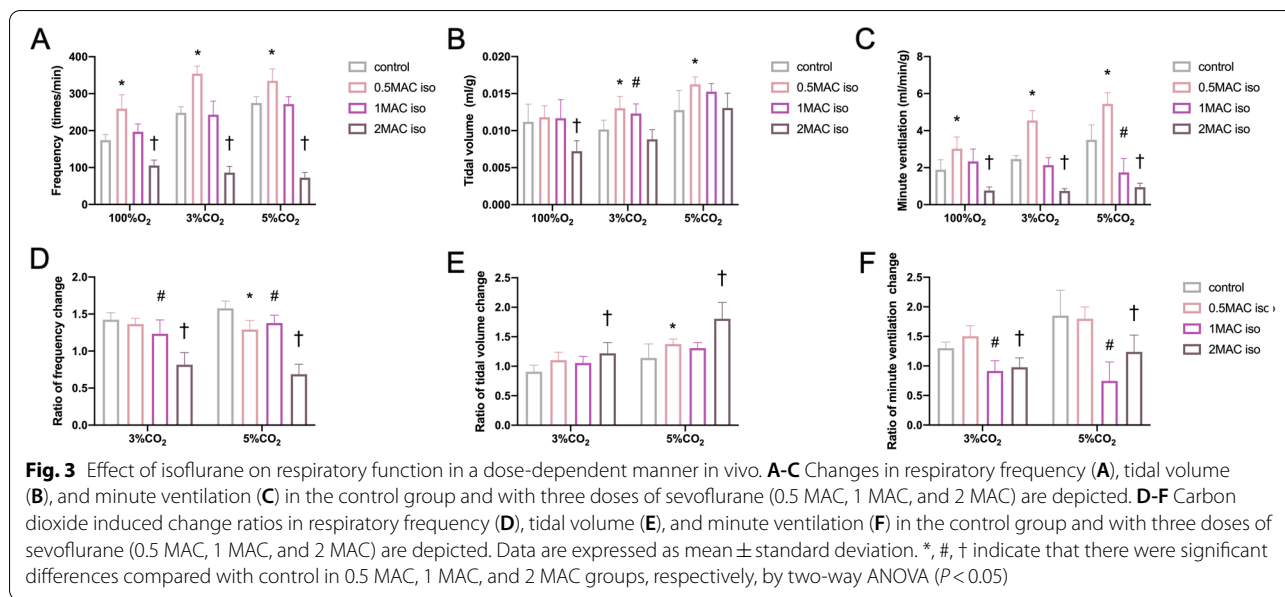
in FR from 100% O₂ to 5% CO₂ (Fig. 5. D, $P=0.023$), but not TV (Fig. 5. E, $P=0.058$) or MV (Fig. 5 F, $P=0.067$).

Inhalational anesthetics cause less respiratory depression compared with intravenous anesthetics

Unlike with inhalational anesthetics, mice administered intravenous anesthetics cannot be accommodated in the chamber in the beginning of the experiment. Mice in the propofol and etomidate groups became hyperactive after i.p. injection outside the chamber. Thus, we compared the stable period of each general anesthetics. We found that at equivalent doses (1 MAC or 1 ED₅₀), sevoflurane and isoflurane caused less respiratory depression compared with propofol and etomidate (Fig. 6 A- 6 L). Propofol caused significant depression in FR, TV and MV after i.p. injection when compared with sevoflurane and isoflurane (Fig. 6 A-C). In addition, we compared Ti, Te, and Ti/Te ratio among the four anesthetics. All four general anesthetics showed an increase in TE. Among them, propofol decreased the Ti/Te ratio ($P < 0.001$ when compared with sevoflurane isoflurane and etomidate groups, Fig. 6D) and increased Te from 0.13 ± 0.01 s to 1.00 ± 0.31 s (Fig. 6K).

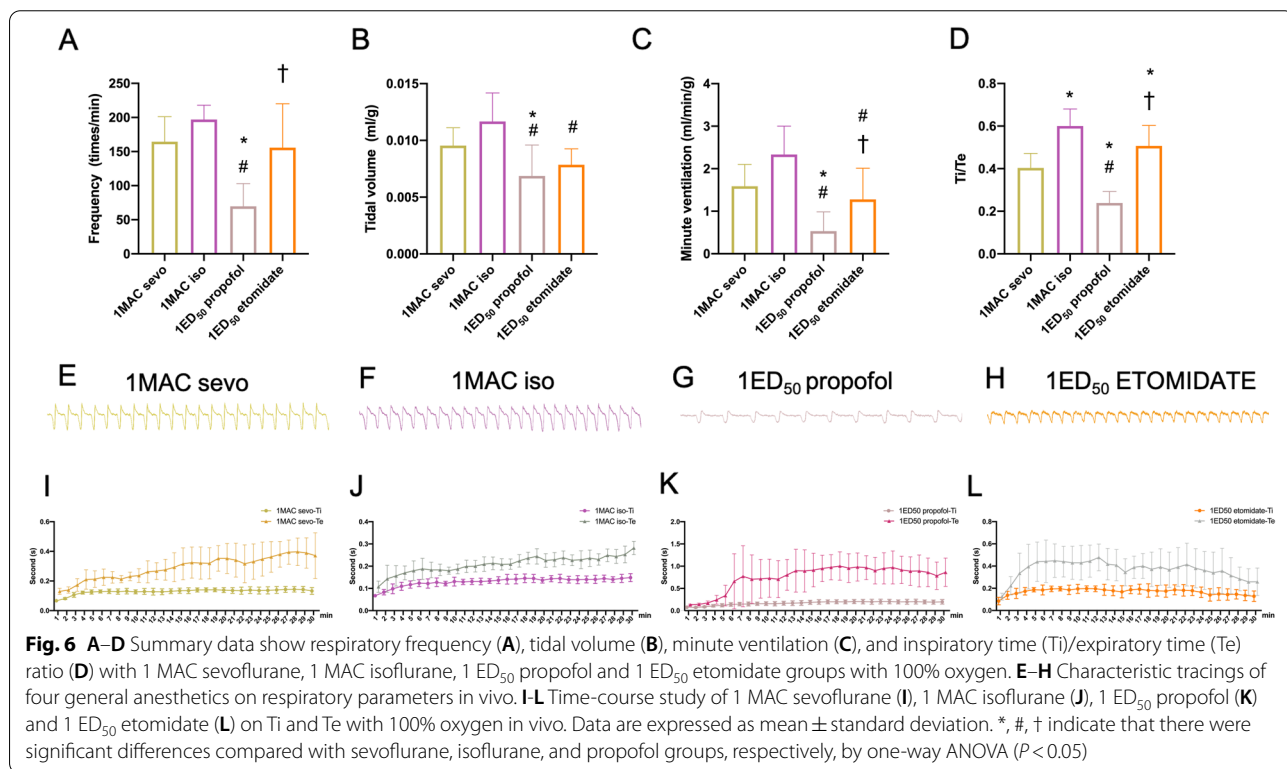
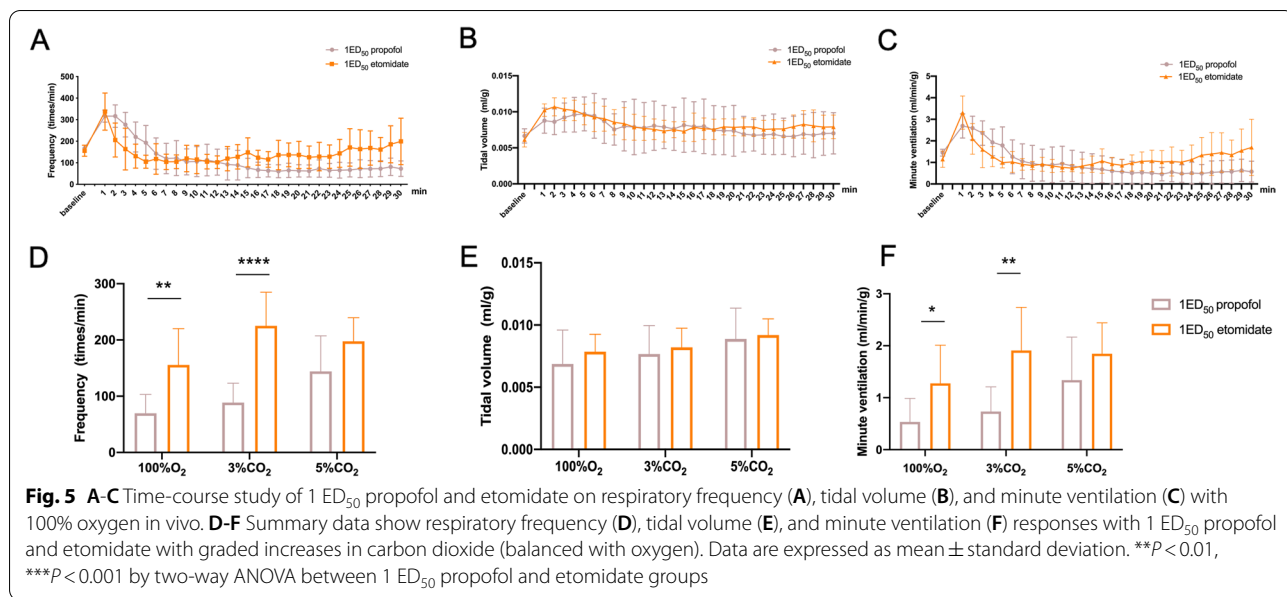
Discussion

In the present study, we found that sub-anesthetic concentrations of sevoflurane and isoflurane increased FR, TV, and MV. In addition, CO₂-sensitive respiratory responses were maintained to a greater degree



with 0.5 and 1 MAC sevoflurane/isoflurane compared with 2 MAC. Meanwhile, in contrast to the etomidate group, propofol showed a dismissed response to graded increases in CO_2 . A time-course analysis revealed that propofol progressively decreased TI/TE ratio during a 30-min exposure compared with sevoflurane, isoflurane, and etomidate at equivalent doses.

In this study, the respiratory response of adult mice to general anesthetics was measured with WBP. WBP is widely used for precise, non-invasive, quantitative measurement of respiratory parameters in unrestrained conditions without intubation [19, 20]. Adult mice were administered sevoflurane, isoflurane, propofol, and etomidate in vivo at doses of 0.5-, 1.0-, and 2.0-times



the MAC or ED₅₀ required to induce LORR, which included the most commonly used dose ranges of inhalational and intravenous anesthetics. In addition, only the state of immobile respiratory parameters was observed with a sufficient duration for subsequent data analysis. The effect of general anesthesia on the CO₂-sensitive

respiratory response was also determined. Concentrations of sevoflurane and isoflurane were monitored in real-time using the RGM monitor to prevent drug and CO₂ accumulation.

General anesthetics modulate ventilation by disturbing central chemoreceptor sensitivity, reducing the

ventilatory response to hypercapnia, depressing metabolic ventilatory control, and inhibiting the ventilatory adaptation to hypoxia, even at sedative doses [7, 8]. In the present study, both sevoflurane and isoflurane preserved spontaneous breathing and the ventilatory response to hypercapnia at sub-anesthetic concentrations. However, higher CO₂ sensitivity was not observed in mice administered 2 MAC sevoflurane/isoflurane. Although multiple sites contribute to the depressive effect of general anesthetics on respiration, the relatively selective maintenance of spontaneous breathing is poorly known. Central CO₂ chemo-sensitivity in mammals is mainly mediated by Phox2B-expressing neurons of the RTN, which were first known for their CO₂/pH sensitivity and role in providing central chemoreceptor drive to the respiratory system [21–23]. Their CO₂ sensitivity is unaffected by pharmacological blockade of the respiratory pattern generator and persists without carotid body input [22]. Volatile anesthetics cause activation of RTN neurons, which serve an important integrative role in maintaining respiratory motor activity under immobilizing anesthetic conditions [24]. Depression by propofol may be attributed to an exclusive effect within the central chemoreflex loop at central chemoreceptors. In contrast to sub-concentrations of inhalational anesthetics, the peripheral chemoreflex loop, when stimulated with CO₂, remains unaffected by propofol [25].

Previous studies demonstrate that sevoflurane-induced respiratory depression is mediated by medullary respiratory and phrenic motor neurons. γ -Aminobutyric acid type A (GABA_A) receptors may be involved in sevoflurane-induced respiratory depression within the medulla, but not within the spinal cord [13, 26]. Many neuronal elements within the respiratory system are inhibited by inhalational anesthetics. The mammalian pre-Bötzinger complex is an excitatory network of neurons in the medulla that is critically involved in respiration [27]. The effect of inhalational anesthetics on TASK-like channels plays a major functional role in chemosensory modulation of respiratory rhythm in the pre-Bötzinger complex [28]. However, these reported mechanisms have not yet elucidated the difference between the effects of isoflurane and sevoflurane.

In the present study, propofol displayed more obvious respiratory depression on FR, TV, and MV compared with etomidate and volatile anesthetics. Propofol at 1 ED50 exhibited rapid and significant respiratory depression approximately 3 min after i.p. injection compared with 1 ED50 etomidate in our study. Propofol also induced the greatest decrease in TI/TE ratio among the four general anesthetics. Propofol may cause significant airway obstruction [29]. Sedative doses of propofol cause a phase shift between abdominal and ribcage movements

under spontaneous breathing without airway support (like the WBP method in our study), thereby decreasing the contribution of ribcage movement to TV and disturbing arterial oxygen tension [30]. It is likely that GABA_A receptor-mediated hyperpolarization of neurons serves as the neuronal basis of propofol-induced respiratory depression *in vivo* [31, 32]. Our study provides new insight into the effect of general anesthetics on respiratory behavior, but further study is needed to uncover the underlying mechanisms. One limitation of our study is that we did not include other types of general anesthetic and analgesics, such as ketamine and opioids.

Conclusion

In conclusion, the present study systematically investigated modulation of respiratory function by general anesthetics and revealed that sevoflurane and isoflurane increase respiratory parameters, even at sub-anesthetic concentrations. Propofol and etomidate depressed TV, but not FR, at higher doses. In addition, propofol induced the greatest decrease in TI/TE ratio among the four general anesthetics. These results suggest that in cases requiring maintenance of spontaneous respiration, sevoflurane or isoflurane may be a better choice than propofol or etomidate.

Abbreviations

CO₂: Carbon dioxide; ED50: Median effective dose; FR: Respiratory frequency; GABA_A: γ -Aminobutyric acid type A; LORR: Loss of the righting reflex; MAC: Minimum alveolar concentration; MV: Minute ventilation; O₂: Oxygen; PaCO₂: Partial pressure of CO₂ in artery; RTN: Retrotrapezoid nucleus; Ti: Inspiratory time; Te: Expiratory time; TV: Tidal volume; WBP: Whole-body plethysmography.

Acknowledgements

We thank Yangyang Wang from West China Medical College of Sichuan University for her help in the behavioral test. We thank Emily Woodhouse, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Authors' contributions

Xuechao Hao: Methodology, Formal analysis, Project administration, Writing—original draft. Mengchan Ou: Methodology, Funding acquisition, Supervision, Writing—review & editing. Yu Li: Resources, Supervision, Validation. Cheng Zhou: Writing—review & editing, Funding acquisition, Methodology. The authors read and approved the final manuscript.

Funding

This work was supported by grant No. 82001183 (to Dr. Ou) from National Natural Science Foundation of China. This work was also supported by the grant No. 2020YJ0052 (to Dr. Hao) from the Science and Technology Department of Sichuan Province; grant No. 2019-I2M-5-011 (to Dr. Hao) from Medicine & Health Innovation Program of the Chinese Academy of Medical Science and grant No. 19HXBH064 (to Dr. Ou) from Post-Doctor Research Project, West China Hospital, Sichuan University; the scientific research fund of the Science and Technology Department of Sichuan province (Grant No. 2018SZ0113 to Dr. Hao).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author (Yu Li) on reasonable request.

Declarations**Ethics approval and consent to participate**

All protocols were approved by the Institutional Animal Experimental Ethics Committee of Sichuan University (Chengdu, Sichuan, China) in accordance with the animal care guidelines of the National Institutes of Health. The study was carried out in compliance with the ARRIVE guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 17 February 2021 Accepted: 28 August 2021

Published online: 06 October 2021

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