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作成者（著者）	Kambayashi, Ryuichi / Goto, Ai / Shinozaki, Makoto / Nakata, Hideo / Izumi-Nakaseko, Hiroko / Takei, Yoshinori / Matsumoto, Akio / Sugiyama, Atsushi
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In vivo Canine Evaluation of Ventilatory Function of a Newly-Developed, Mechanically-Assisted, Bag-Valve Ventilator: Comparison with That of a Commonly-Used, Piston-Driven, Volume-Limited, Animal Ventilator

Ryuichi Kambayashi[1)] Ai Goto[1)] Makoto Shinozaki[1)]
Hideo Nakata[2)] Hiroko Izumi-Nakaseko[1)] Yoshinori Takei[1)]
Akio Matsumoto[3)] and Atsushi Sugiyama[1, 3)]*

[1)]Department of Pharmacology, Faculty of Medicine, Toho University, Tokyo, Japan
[2)]TSS HEALTHCARE Co., Ltd., Tokyo, Japan
[3)]Department of Aging Pharmacology, Faculty of Medicine, Toho University, Tokyo, Japan

ABSTRACT: Ventilatory function of a newly-developed, mechanically-assisted, bag-valve ventilator was assessed in dogs. After general anesthesia was introduced using isoflurane inhalation with a commonly-used, piston-driven, volume-limited, animal ventilator, the inhalation was terminated. Then, the animal was ventilated with room air using either the piston-driven ventilator (n = 5) or the mechanically-assisted, bag-valve ventilator (n = 5). No lethal respiratory failure or hemodynamic collapse was induced by either of the ventilations. Time course of the changes in oxygen saturation was similar between the ventilations, suggesting that the bag-valve ventilator may allow adequate inspiration comparable to the piston-driven one. Moreover, the heart rate and mean blood pressure increased similarly by those ventilations, reflecting gradual attenuation of the isoflurane-induced negative chronotropic and hypotensive effects, which indicates that the bag-valve ventilator may permit necessary expiration comparable to the piston-driven one. Thus, the mechanically-assisted, bag-valve ventilator could become an alternative to commonly-used ventilators.

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KEYWORDS: bag-valve, dogs, hemodynamics, isoflurane, ventilator

Introduction

Bag-valve mask is commonly used to manually provide positive pressure ventilation to sick and/or injured subjects in emergency care, which basically consists of a bag (air chamber), a unidirectional valve, an expiratory port, and a connector to the subject.[1)] The unidirectional valve enables to prevent expiratory air from flowing back into the bag and to provide inspiratory air to subjects only when the bag is compressed.[1)] A bag-valve mask is less expensive compared with a standard artificial ventilator. Moreover, a bag-valve mask can be available outside of hospital, whereas standard artificial ventilators are largely used inside of hospital.[2)] Meanwhile, the limitation of a bag-

*Corresponding Author: Atsushi Sugiyama, 5-21-16 Omori-nishi, Ota-ku, Tokyo 143-8540, Japan, tel: +81–3–3762–4151 (Ext 2361)
e-mail: atsushi.sugiyama@med.toho-u.ac.jp
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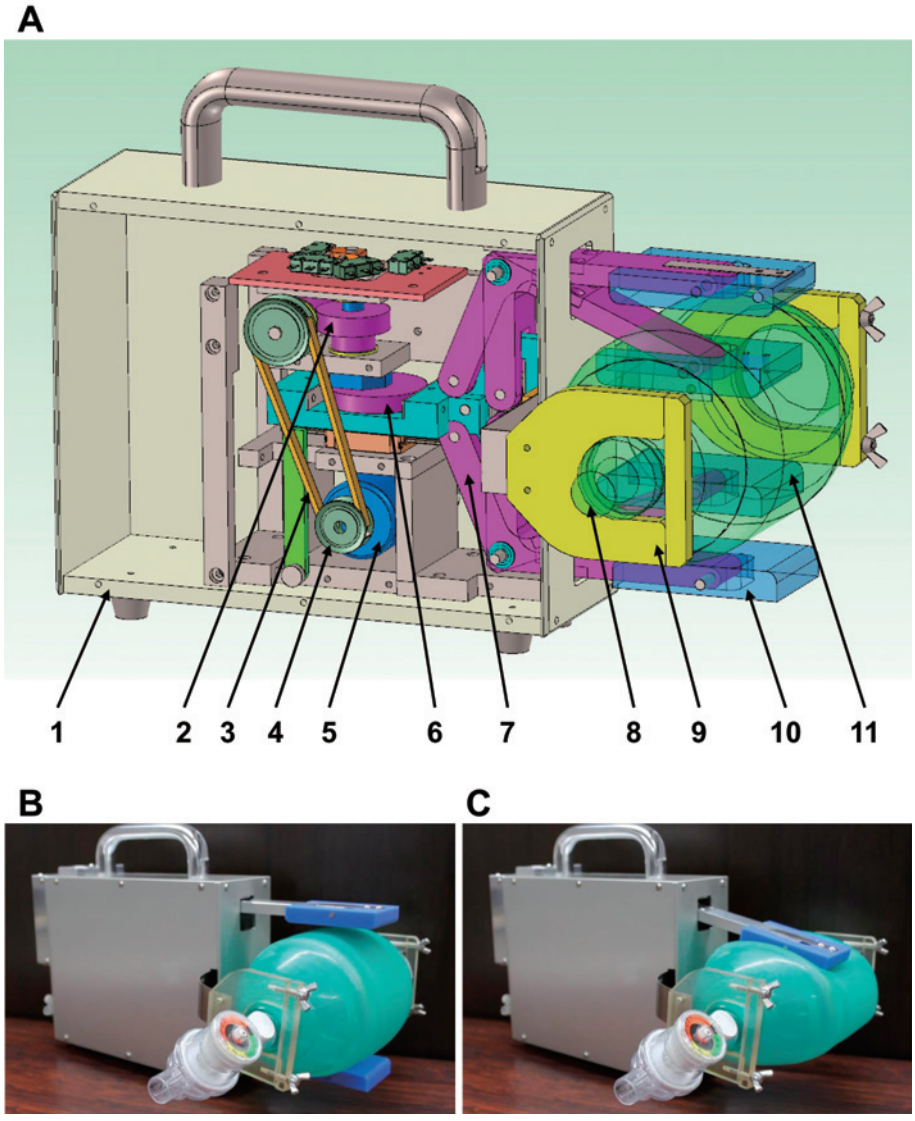

Fig. 1
System of the mechanically-assisted device for bag-valve ventilation. The device consists of 1) case, 2) worm gear, 3) driving belt, 4) belt pulley, 5) motor, 6) driving cam, 7) driving link, 8) connecting port to unidirectional valve, 9) supporter, 10) compression plate, and 11) bag (air chamber) (A). Photos of the device during the decompression phase (B) and compression phase (C).

valve mask may include that practitioner must keep on rhythmically compressing the bag with holding the mask in place on the face of the subjects.[2] More importantly, bag-valve mask ventilation operated by an untrained practitioner can damage the lungs of the subjects by over compression of the bag.[2]

Coronavirus disease 2019 (COVID-19) induced acute respiratory distress syndrome requiring intensive respiratory support, which has markedly increased the demand for use of ventilators to manage COVID-19 patients.[3,4] Indeed, a shortage of artificial ventilators was reported in many countries.[2–4] To overcome such a difficult situation, Massachusetts Institute of Technology (MIT) team designed a simple and inexpensive ventilator device to mechanically-assist the bag-valve mask ventilation, which was published as an open source.[5] MIT team mentioned that the approval of a device by the regulatory authority should be sought by a manufacturer that ultimately adapts and makes the device inspired by the open-source reference material.[5] By utilizing the concept, we developed a mechanically-assisted device for bag-valve ventilation (the bag-valve ventilator) (Fig. 1), ultimately aiming at

its clinical application.

The performance of bag-valve mask ventilators has been studied mainly using manikin-based simulators; however, their accuracy and reproducibility are limited due to a lack of in situ airway anatomy and physiology in the living body.[6, 7] To begin to facilitate the clinical development of the bag-valve ventilator, we adopted the isoflurane-anesthetized dogs, in which its impacts on the essential respiratory and cardiovascular variables were assessed including the SpO_2, heart rate, and mean blood pressure. As for the study design of the ventilator function test, both the recovery speed from the isoflurane inhalation-induced suppression of spontaneous breathing and the time courses of SpO_2, heart rate, and blood pressure were used as surrogate markers for estimating the ventilatory efficiency of the bag-valve ventilator. Furthermore, we compared them with those of a commercially available, piston-driven, volume-limited, animal ventilator (the piston-driven ventilator).

Methods

Preparation of experiment

Experiments were performed using female beagle dogs weighing approximately 9 kg (n = 5). Animals were obtained through Kitayama Labes Co., Ltd. (Nagano, Japan). The animals were individually housed in stainless steel cages on a 12 h light (6:00-18:00)-dark (18:00-6:00) cycle, and were given 200 g/day of pellet diet (CD-5M, CLEA Japan Inc., Tokyo, Japan) and free access to tap water. The animal room was maintained at a temperature of 23 ± 2°C and a relative humidity of 50 ± 20%. The dogs were initially anesthetized with thiopental sodium (30 mg/kg, i.v.). After intubation, anesthesia was maintained by isoflurane inhalation (1.5% v/v) vaporized in oxygen using the piston-driven, volume-limited, animal ventilator (SN-480-3; Shinano Manufacturing Co., Ltd., Tokyo, Japan). The ventilatory volume, rate, and inspiratory/expiratory ratio were set at 200 mL/time, 15 times/min, and 1, respectively for each animal. We did not set positive end-expiratory pressure for the bag-valve ventilator or the piston-driven one in this study. A pulse oximeter probe was placed attached to the tongue to measure oxygen saturation, which was continuously monitored along with the surface lead II electrocardiogram and arterial blood pressure at the right femoral artery.

Experimental protocol

After confirming that the heart rate and aortic pressure became stable for >5 min with their variations of <5% and that stage 3 level of anesthesia (surgical anesthesia) was attained, the isoflurane inhalation was stopped, and then the animal was ventilated with room air using the piston-driven ventilator. When the spontaneous breathing followed by body movement occurred, the animal was judged to be recovered from stage 3 to stage 2 level of anesthesia (excitement). When such the recovery of anesthesia was observed or 30 min of observation period was over, the animal was anesthetized again with isoflurane inhalation (1.5% v/v) for >30 min. After confirming the stable heart rate and aortic pressure and that stage 3 anesthesia was attained again, the isoflurane inhalation was stopped and the ventilation with room air was started using the bag-valve ventilator. The recovery from the anesthesia was assessed in the same manner as that for the piston-driven ventilator. After the experiment, we kept the animal for >2 weeks with the highest standard of health management and dietary control.

Statistical analyses

Differences within a parameter were evaluated with paired *t*-test or two-way, repeated-measures analysis of variance followed by Fisher's least significant difference test as a post hoc-test for the comparison of mean values. The time course of changes in the probability of animals under the anesthesia was depicted with Kaplan-Meier curve, which was compared by log-rank test. GraphPad Prism 8 (ver. 8.43; GraphPad Software, LLC, La Jolla, CA, USA) was used. A *p*-value of <0.05 was considered to be significant.

Results

No animals exerted any lethal respiratory failure or hemodynamic collapse leading to their death during the experimental period. No abnormal physical finding related to respiration was noticed in any of the animals after the study.

Recovery from anesthesia

The Kaplan-Meier curves showing the probability of animals under anesthesia after the start of the piston-driven ventilation and the bag-valve one with room air are depicted in Fig. 2. Four out of five dogs were recovered from stage 3 to stage 2 level of anesthesia by the piston-driven ventilator with room air, which was observed at 19 min (#2), 20 min (#4), 21 min (#1), and 21 min (#5), whereas the remaining dog (#3) was not done for 30 min. On the other hand, each animal was recovered from stage 3 to

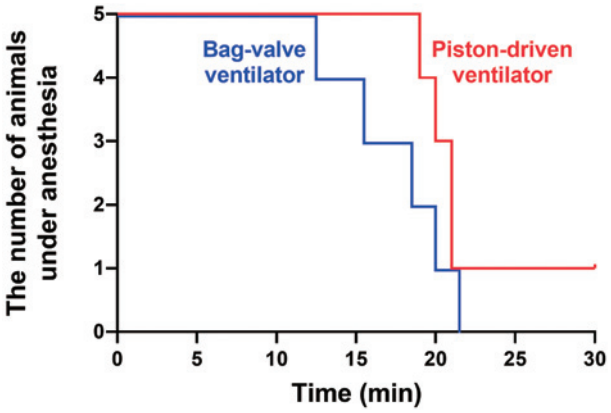

Fig. 2
Kaplan-Meier curves showing the time courses of changes in the probability of animals under anesthesia after the start of room-air ventilation using the piston-driven, volume-limited, animal ventilator (Piston-driven ventilator, red, n = 5) and the mechanically-assisted, bag-valve ventilator (Bag-valve ventilator, blue, n = 5).

stage 2 level of anesthesia by the bag-valve ventilator with room air, which was observed at 12.5 min (#2), 15.5 min (#1), 18.5 min (#4), 20 min (#3), and 21.5 min (#5). No significant difference in the Kaplan-Meier curves was detected between the treatments (Fig. 2).

Time course of oxygen saturation, heart rate and mean blood pressure

Since the animal started to be recovered from anesthesia at 12.5 min after the start of ventilation with room air (Fig. 2), the time courses of values of oxygen saturation, heart rate and mean blood pressure from 5 min before (−5 min) to 12.5 min after the ventilation with room air were compared between the piston-driven ventilator and the bag-valve ventilator treatments (Fig. 3). Their basal control values at −5 min were 98.8±0.2%, 93±4 bpm, and 120 ± 4 mmHg in the piston-driven ventilator treatment, whereas those were 98.8 ± 0.2%, 97 ± 3 bpm, and 123 ± 4 mmHg in the bag-valve ventilator treatment, respectively. No significant difference was detected in those basal control values between the treatments.

The piston-driven ventilation with room air decreased the oxygen saturation at 8 min, for 9-9.5 min and for10.5-12.5 min, increased the heart rate for 7-12.5 min, and elevated the mean blood pressure for 1.5-12.5 min (Fig. 3, red symbols). Meanwhile, the bag-valve ventilation with room air decreased the oxygen saturation for 4-7.5 min and for 8.5-12.5 min, increased the heart rate for 4-12.5 min, and elevated the mean blood pressure for 1.5-12.5 min (Fig. 3, blue symbols). No significant difference in the time courses of the three variables was detected between the treatments (Fig. 3). The decrease in oxygen saturation below 85% was not observed in any of the animals until 30 min after the start of ventilation with room air in either treatment (not shown in the figure).

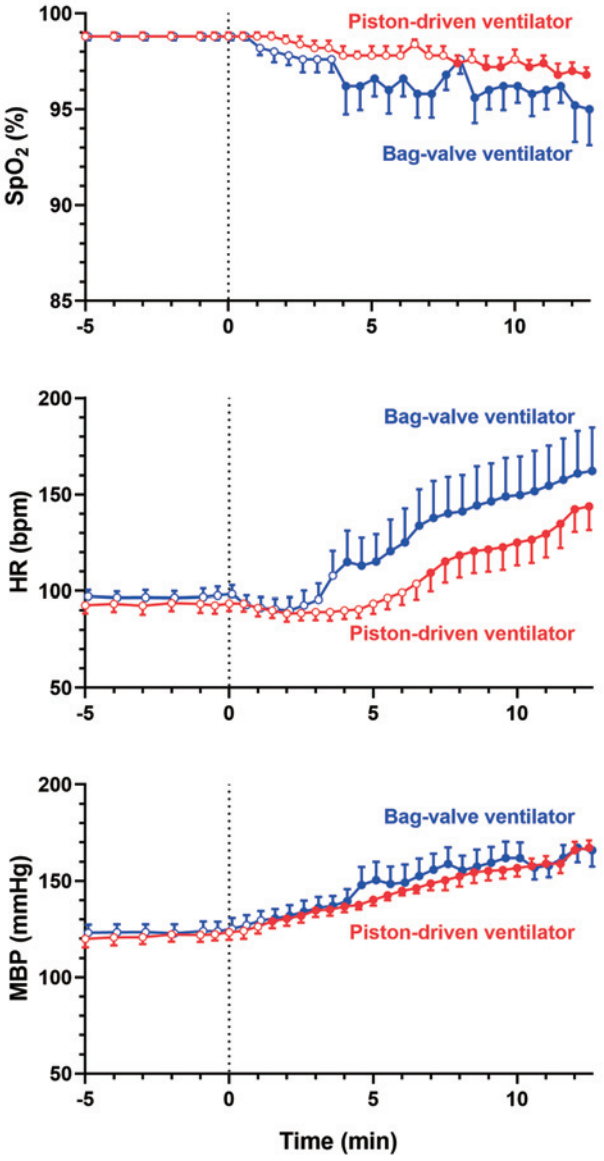

Fig. 3
The time courses of changes in the oxygen saturation (SpO_2), heart rate (HR), and mean blood pressure (MBP) during room-air ventilation with the piston-driven, volume-limited, animal ventilator (Piston-driven ventilator, red, n = 5) and the mechanically-assisted, bag-valve ventilator (Bag-valve ventilator, blue, n = 5). Data are presented as mean ± SE. Filled symbols represent statistically significant differences from each value at 5 min before the start of ventilation with room air (−5 min) by $p < 0.05$.

Discussion

In this study, we tried to estimate the utility and safety of the newly-designed, mechanically-assisted, bag-valve ventilator in vivo, preparing for a shortage of artificial ventilators and/or well-trained practitioners when COVID-19 becomes pandemic.[2–4] We observed interesting and promising findings as described below.

The time courses of recovery from anesthesia were compared between the piston-driven ventilation and the bag-valve ventilation using the anesthetized dogs. After switching from the inhalation of 1.5% isoflurane to room air, each of the ventilations showed a similar time course of changes in the oxygen saturation without inducing hemodynamic collapse, indicating that the bag-valve ventilation may allow adequate inspiration comparable to the piston-driven one. Moreover, the heart rate and mean blood pressure increased similarly by those ventilations, reflecting gradual attenuation of the isoflurane-induced negative chronotropic and hypotensive effects,[8–11] which indicates that the bag-valve ventilator may permit necessary expiration comparable to the piston-driven one.

The asynchronous ventilation associated with spontaneous breathing[12] was more frequently observed in the bag-valve ventilation than in the piston-driven one, and recovery from the anesthesia was slightly earlier with the former (Fig. 2). Similarly, the bag-valve ventilator decreased the SpO_2 but increased the heart rate earlier than the piston-driven one before the recovery from anesthesia (Fig. 3), also indicating that undetectable level of asynchronous ventilation associated with spontaneous breathing might have occurred more in the former before we noticed typical asynchronous ventilation. Note that the tidal volume of the bag-valve ventilator may change depending on the intratracheal resistance of the animals more largely than that of the piston-driven one due to compliance of the bag. Current findings suggest that net tidal volume might be greater with the bag-valve ventilator than that with the piston-driven one; namely, the former may have more effectively replaced the isoflurane in the lung with a room air than the latter, leading to earlier recovery from the anesthesia.

There are some limitations in this study. First, only one order of ventilation treatment; namely, the piston-driven ventilator followed by the bag-valve one, was evaluated, since the dogs were anesthetized with the piston-driven ventilator just before the cessation of isoflurane inhalation. The reverse order may need to be done to further confirm the current observation. Second, macroscopic or microscopic morphological evaluation of lung tissue was not performed. Although no abnormal physical finding was noticed after the experiment, the extensive evaluation of lung tissue after relatively longer use of the ventilator will be required before the clinical application of the bag-valve ventilation. Third, the chemoreceptor reflexes may have influenced the recovery rate from anesthesia with isoflurane inhalation, which could be estimated by objective indices including the tidal volume and CO_2 as well as isoflurane concentration in the blood or exhaled air.

In conclusion, the bag-valve ventilator may allow adequate inspiration and expiration comparable to the piston-driven one without inducing any adverse event after terminating isoflurane inhalation, indicating that the mechanically-assist device can help overcome the limitation of bag-valve-mask ventilation. Thus, the mechanically-assisted, bag-valve ventilator could become a less expensive alternative to commonly-used standard ventilators.

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Authors' contribution: R.K. and A.S. conceived and designed the research. R.K., A.G., and M.S. conducted experiments and analyzed data. R.K. and A.S. wrote the manuscript. All authors read, discussed, and approved the manuscript.

Ethics statement: The experiments were approved by the Toho University Animal Care and User Committee (No. 21-51-489 and 22-52-489) and performed according to the Guideline for the Care and Use of Laboratory Animals of Toho University.

Conflicts of interest: H.N. was an employee of TSS HEALTHCARE Co., Ltd. A.S. received research funds from TSS HEALTHCARE Co., Ltd., for joint research. The other authors declare no relevant conflicts of interest.

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