Marathoners' Breathing Pattern Protects Against Lung Injury by Mechanical Ventilation: A Pilot Study

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Abstract

Background Breathing during a marathon is often done empirically in a so-called “2:2 breathing rhythm”. This breathing rhythm is based on cycles composed of four phases: the 1st inspiratory period, 2nd inspiratory period, 1st expiratory period, and, finally, the 2nd expiratory period. We developed a prototype ventilator that can perform intermittent positive pressure ventilation, mimicking the breathing cycle of the 2:2 breathing rhythm. This mode of ventilation was named the marathoners’ breathing rhythm ventilation (MBV) and we hypothesized that MBV may have a lung protective effect.

Methods We examined the effects of the MBV on the pulmonary pre-edema model in isolated perfused rabbit lungs. The pulmonary pre-edema state was induced using bloodless perfusate with low colloid osmotic pressure. The fourteen isolated rabbit lung preparations were randomly divided into the inversed ratio ventilation (IRV) group and the MBV group, (both had an inspiratory:expiratory ratio of 1:1). In the IRV group, seven rabbit lungs were ventilated using a Harvard Ventilator 683 with a tidal volume (TV) of 8 mL/kg, a respiratory rate (RR) of 30 cycles/min, and a positive-end expiratory pressure (PEEP) of 2 cmH_2O for 60 min. In the MBV group, seven rabbit lungs were ventilated using the prototype ventilator with a TV of 6 mL/kg, an RR of 30 cycles/min, and a PEEP of 4 cmH_2O (first step) and 2 cmH_2O (second step) for 60 min. The time allocation of the MBV for one cycle was as follows: 1st inspiratory period, 2nd inspiratory period, 1st expiratory period, and 2nd expiratory period (all 0.3 s long), with intermittent resting periods (all 0.2 s).

Results Peak airway pressure and lung wet-to-dry ratio after 60 min ventilation were lower in the MBV group than in the IRV group.

Conclusion MBV was considered to have a lung protective effect compared to the IRV method.

Background

Breathing during a marathon is often done empirically in a so-called “2:2 breathing rhythm”.[1] This 2:2 breathing rhythm is based on cycles composed of four phases: the 1st inspiratory period, 2nd inspiratory period, 1st expiratory period, and, finally, the 2nd expiratory period. These phases are synchronized with the step rate, e.g., a step with the left foot coincides with the 1st inspiration and 1st expiration phase. Matching rhythmic steps with inspiration and expiration means that the inspiratory:expiratory (I:E) ratio is 1:1 for the 2:2 breathing rhythm.

Mechanical ventilation causes lung damage, a pathological condition called ventilator-induced lung injury (VILI).[2, 3] VILI is a factor that increases the mortality rate in acute respiratory distress syndrome (ARDS).[2] The main factor that causes VILI is alveolar overdistension (volutrauma) and cyclic reopening of collapsed alveoli (atelectrauma).[4] The ventilation strategy to protect the lungs against deterioration in ARDS is to prevent additional volutrauma and atelectrauma of the remaining normal lung tissue.[5] Recently, low tidal volume (TV) ventilation has been established as a lung-protective ventilation strategy;

however, it has the disadvantage of $PaCO_2$ retention.[6] Other possible lung-protective ventilation strategies include inversed ratio ventilation (IRV)[7] and high-frequency oscillatory ventilation (HFOV).[8]

During exercise, there is a risk of hypoxemia and pulmonary edema.[9-11] In intense exercise, cardiac output increases as the demand for O_2 increases, and the right ventricular pressure and pulmonary artery pressure rise.[12] The effectiveness of the 2:2 breathing rhythm on cardiopulmonary function during a marathon has not yet been proven in a study. However, the 2:2 breathing rhythm is empirically favored in marathon runners, presumably because it prevents the progression of additional hypoxemia and pulmonary edema during the marathon. Moreover, since CO_2 is not retained during a marathon, where the metabolism is increased over an extended time, it has been suggested that the 2:2 breathing rhythm provides sufficient capacity for CO_2 elimination.[13]

In the present study, we developed a prototype ventilator that can perform intermittent positive pressure ventilation, mimicking the breathing cycle of the 2:2 breathing rhythm (Fig. 1). This mode of ventilation was named the marathoners' breathing rhythm ventilation (MBV) and is a mechanical ventilation method that divides the TV required for conventional mechanical ventilation into the inspiratory volume of the 1st and 2nd inspiratory periods. Since the prototype ventilator was designed to deliver a constant inspiratory flow rate, and the durations of the 1st and 2nd inspiratory periods were set to be the same, the inspiratory volumes of the two periods were equal. Thus, each inspiratory volume can be reduced in the MBV. In addition, the MBV had an I:E ratio of 1:1. Therefore, MBV can be considered as a ventilation mode that combines the features of low TV ventilation and IRV.

In this paper, the following are reported: 1) the manufacture of the prototype ventilator capable of MBV, and 2) the effects of the MBV on the pulmonary pre-edema model, which were compared with those of the IRV (I:E ratio 1:1) in isolated perfused rabbit lungs. The pulmonary pre-edema state was induced by using bloodless perfusate with low colloid osmotic pressure.

In the MBV method, the 1st inspiratory, 2nd inspiratory, 1st expiratory, and 2nd expiratory phases taken together defined one cycle. In the IRV method, the inspiratory and subsequent expiratory phase together defined one cycle. In both MBV and IRV methods, TV was defined as the total ventilation volume during one cycle. In both MBV and IRV methods, the unit of respiratory rate (RR) was cycles/min.

Materials And Methods

All experimental protocols regarding the use and care of animals in the present study were approved by the Laboratory Animal Care Committee of the Faculty of Medicine at Tottori University (approval number: 10-Y-13). Adult female Japanese white rabbits (2.2–3.1 kg) were purchased from Oriental Yeast Co. (Tokyo, Japan). The rabbits were kept under standard housing conditions with free access to food and water.

Materials

Manufacture of the prototype ventilator

We created a prototype ventilator that can perform intermittent positive pressure ventilation and mimic the breathing cycle of the 2:2 breathing rhythm during a marathon (Fig. 1). The prototype ventilator is a combination of digital timers, solenoid valves, and existing respiratory equipment (ACOMA AR-300, Acoma Co., Tokyo, Japan). The ACOMA AR-300 is a volume-limited, time-cycling ventilator, in which the I:E ratio can be adjusted from 1:3 to 3:1, and the TV can be set from 20 to 300 mL. The ACOMA AR-300 is a piston-driven ventilator, designed to deliver a constant inspiratory flow rate. The I:E ratio of the ACOMA AR-300 was set to 1:1. The detector switch was attached to the piston rod of the ACOMA AR-300 and the switch was set to emit a signal each time it detected the start of the inspiratory period of the ventilator. The signal was sent to four digital timers (H5BR-B, Omron Co., Tokyo, Japan). Each of these timers was connected to a solenoid valve: three tri-directional valves (VDW350-6G-3-01, SMC Co., Tokyo, Japan) and one bidirectional valve (VDW31-6G-3-01, SMC Co.). These four solenoid valves were powered by 12-Volt DC supplied by the connected digital timer. All digital timers were reset as soon as the ACOMA AR-300 inspiratory start signal was received, at which point they started to measure elapsed time. The start time and duration of the 12-Volt DC output (controlling the solenoid valves) could be set individually for each of the four digital timers.

A schematic diagram of the prototype ventilator is shown in Fig. 1A, and Fig.1B is an example of the time allocation for the four solenoid valves with the RR set to 30 cycles/min. An example of the solenoid valve operation and the corresponding inspired and expired gas dynamics follow. One cycle was defined as the sum of eight separate actions: the 1st inspiratory period, a resting period, the 2nd inspiratory period, a resting period, the 1st expiratory period, a resting period, the 2nd expiratory period, and a final resting period. In this example, the respiration rate of the ACOMA AR 300 was set to 30 breaths/min. In response to the inspiratory start signal of the ACOMA AR 300, all digital timers were reset and began to record the time. First, the solenoid valve #1 opened for 0.3 s, and air from the ventilator flowed directly into the inspiratory circuit (1st inspiratory period: 0.3 s). When solenoid valve #1 closed, the air moved towards solenoid valve #2, but since solenoid valve #2 was closed, the air was released into the atmosphere from the exhaust pipe (resting period). After 0.5 s from the start signal, solenoid valve #2 was opened for 0.3 s, and the air from the ventilator went into the inspiratory circuit again (2nd inspiratory period: 0.3 s). When solenoid valve #2 was closed, the air was released into the atmosphere from the exhaust pipe of solenoid valve #2 (resting period). After 1.0 s from the start signal, solenoid valve #3 was opened for 0.3 s, and expired gas was released from the exhalation pipe of this valve into the atmosphere (1st expiratory period: 0.3 s). When solenoid valve #3 was closed, the expired gas moved towards solenoid valve #4, but since solenoid valve #4 was closed, the emission of the expired gas into the atmosphere was interrupted (resting period). After 1.5 s from the start signal, solenoid valve #4 was opened for 0.3 s, and the expired gas was released from the exhalation pipe of solenoid valve #4 into the atmosphere (2nd expiratory period: 0.3 s). When solenoid valve #4 was closed, the emission of the expired gas into the atmosphere was interrupted (resting period). Two seconds after the start signal, the detector switch detected the next

inspiratory cycle of the ACOMA AR 300, the digital timer was reset, and the MBV breathing cycle was repeated. In this example, it did not matter if the open duration of solenoid valve #4 was set to values above 0.5 s, because the detector switch detected the start of the next inspiratory cycle in the ACOMA AR 300. This terminated the open duration of valve #4 since the reset of the digital timers was prioritized, thus the actual open duration of solenoid valve #4 was 0.5 s.

With this prototype ventilator, producing mechanical ventilation in a 2:2 breathing rhythm, the RR can be adjusted in 5 cycles/min increments from 10 cycles/min to 65 cycles/min. In addition, the positive end-expiratory pressure (PEEP) can be set at arbitrary pressure values independently of the exhaust pipes of the solenoid valves #3 and #4. The ventilation volume of one MBV cycle is the difference between the TV set in the ACOMA AR 300 and the exhaust volume from the exhaust pipe of solenoid #2. Since this ventilator is in the prototype stage, the ventilation volume of one MBV cycle has to be determined from the average gas volume of several expiratory cycles collected by the classical water displacement method.[14]

Preliminary study

In rabbits in vivo (n = 9), a preliminary experiment was conducted on the physiological effects of the MBV method on intact lungs. The rabbits were tracheostomized, anesthetized with pentobarbiturate, and paralyzed with pancuronium bromide. We measured arterial blood gas values, TV, minute volume, RR, airway pressure, etc. during the MBV method and the IRV method (both I:E ratio of 1:1).

Figure 2 shows the above-mentioned outcomes of each parameter in a radar chart. Normalization was performed using each average value of the IRV method. The pH was expressed by the hydrogen ion concentration. Compared to the IRV method, the MBV method was expected to effectively eliminate carbon dioxide with a smaller amount of TV and minute volume. In this preliminary study each rabbit was assessed with both ventilation methods, however we did not test for significant differences in the mean values between the methods since the order of testing was not randomized.

Figure 3 displays typical waveforms of the airway pressure for both mechanical ventilation methods with a PEEP of 0 cmH_2O in the same rabbit. The waveform in Fig. 3A describes the airway pressure in the IRV method, whereas Fig. 3B presents the airway pressure curve in the MBV method. In the MBV method, the airway pressure transiently decreased immediately after the end of the 1st inspiratory period and transiently increased immediately after the end of the 1st expiratory period.

Isolated perfused lung preparation

We compared the effect of MBV with IRV on pre-pulmonary edema in isolated perfused rabbit lungs. The isolated perfused rabbit lungs were prepared using the method described in detail by Liu et al.[15] with

minor modifications. Briefly, the rabbits were anesthetized with pentobarbital 30 mg/kg intravenously, followed by ketamine 25 mg/kg intramuscularly, and anticoagulation with heparin 500 u/kg intravenously. After local anesthesia of the anterior neck and the sternum region with 1% lidocaine, tracheal intubation was performed through a tracheostomy and the rabbits were ventilated mechanically. A median sternotomy was performed, and an incision was made into the right ventricle. The rabbits were euthanized by rapidly exsanguinating whole blood (70 mL) from the incision site in the right ventricle. The pulmonary artery and the left atrium were cannulated via the right and left ventriculotomies, respectively. Finally, the lungs were removed en bloc and enclosed in a humidified chamber.

The lungs were perfused with bicarbonate-buffered physiological salt solution (PSS), which comprised of NaCl, 119; KCl, 4.7; $MgSO_4$, 1.17; $NaHCO_3$, 22.61; KH_2PO_4, 1.18, and $CaCl_2$, 3.2 mM in a recirculating manner. To every 100 mL of PSS stock solution, 100 mg dextrose, 20 mU insulin, 3 g Ficoll® PM70 (GE Healthcare Bio-Sciences, Little Chalfont, UK), and 2 mg indomethacin (Sigma Chemical, St. Louis, MO) were added. Ficoll® PM70 is a high molecular weight sucrose polymer with an average molecular weight of 70 000. If an isolated rabbit lung is perfused with Krebs Ringer solution supplemented with 4% (w/v) albumin without the addition of red blood cells to the perfusate, it will develop pulmonary edema within 2 h.[16] Ficoll® PM70, as well as albumin, provide a normal colloidal osmotic pressure at 4% (w/v).[17] If isolated murine lungs are perfused with Dulbecco's Modified Eagle's Medium containing 4% (w/v) Ficoll® PM70 without the addition of red blood cells to the perfusate, an edema will form in the lung interstitium within 1 h[18]. In the current study, a pulmonary pre-edema model was created in the isolated rabbit lung via perfusion with bicarbonate-buffered PSS containing 3% (w/v) Ficoll® PM70 without the addition of red blood cells to the perfusate.

The perfusate flow rate was gradually increased to 35 mL/kg/min, while the ventilation gas was changed from air to a mixed gas (O_2, 21%; CO_2, 5%; N_2, 74%). The perfusate flow rate was continuously measured with an electromagnetic flowmeter (MF-1200, Nihon Kohden, Tokyo, Japan). The left atrial pressure was set to 4 mmHg by regulating the height of a reservoir connected to the venous circuit. The lungs were ventilated with a TV of 6 mL/kg and a respiratory frequency of 40 breaths/min with a PEEP of 2 cmH_2O using a Harvard Ventilator 683. Blood gases were measured using iSTAT. The perfusate pH was adjusted to 7.40 using an appropriate amount of 1 mM $NaHCO_3$ (Meylon, Otsuka Pharmaceutical, Tokyo, Japan), and the temperature of the perfusate was maintained at 38°C using a regulated heating system. Pulmonary arterial pressure, left atrial pressure, and airway pressure were recorded using a PowerLab system (AD Instruments, New South Wales, Australia; software, Chart ver. 5) with a transducer connected to amplifiers. The isolated perfused lungs were allowed to stabilize for 20 min before proceeding to the experimental protocol.

Experimental protocol

The fourteen isolated rabbit lung preparations were randomly divided into the IRV and MBV groups.

In the IRV group, rabbit lungs (n = 7; body weight, 2.5 ± 0.2 kg) were ventilated using a Harvard Ventilator 683 with a TV of 8 mL/kg, an RR of 30 cycles/min, and a PEEP of 2 cmH_2O for 60 min.

In the MBV group, rabbit lungs (n = 7; body weight, 2.4 ± 0.2 kg) were ventilated using the prototype ventilator with a PEEP of 4 cmH_2O (first step) and 2 cmH_2O (second step) for 60 min. Before the experiment, the TV of the MBV was adjusted to 6 mL/kg using a test lung and measured by the water displacement method.[14] The mixed gas containing 5% CO_2 partially dissolves in water, so the volume of the gas decreases. Therefore, we measured in advance that the decrease in volume after exposure to water for 10 minutes was less than 0.05 mL per 10 mL. The MBV group had a RR of 30 cycles/min, and the time allocation for one cycle had the following pattern: 1st inspiratory period 0.3 s, resting period 0.2 s; 2nd inspiratory period 0.3 s, resting period 0.2 s; 1st expiratory period 0.3 s, resting period 0.2 s; and 2nd expiratory period 0.3 s, resting period 0.2 s.

Peak airway pressure and mean airway pressure

Peak airway pressure (pPaw) and mean airway pressure (mPaw) at the stabilization period (baseline) and after 60min ventilation were calculated based on the values recorded by the PowerLab system.

Pressure volume curve measurement

The inflation pressure volume (PV) curve was measured at the stabilization period (baseline) and after 60 min ventilation using the quasi-static method and a syringe containing mixed gas, while ventilation and perfusion were temporarily removed.[4] This method involved the measurement of airway pressure as the lungs were gradually inflated in 5-mL steps, until a volume of 40 mL is reached. The total inhalation volume was assessed up to 40 mL to prevent injuries caused by the measurement method itself. Each inflation interval was set at 15 s to obtain a plateau pressure. The deflation PV curve was not measured.

Lung wet-to dry ratio

After all the measurements had been completed, the left lung was excised, and its wet weight was measured. It was dried at 60°C in an oven for two weeks, and its dry weight was measured to determine the lung wet-to-dry ratio (W/D) using the formula: W/D = wet weight / dry weight.[15]

Bronchoalveolar lavage fluid analysis

After all the measurements had been completed, the right lung was used for bronchoalveolar lavage fluid (BALF) preparation. Three aliquots (5 mL each) of sterile saline were instilled separately through the trachea and drained. The lavage fluid was centrifuged at 200 × *g* for 10 min at 4°C, and the cell-free supernatant was stored at -70°C as BALF for further chemical analyses.

The BALF was used to measure total protein concentration and myeloperoxidase (MPO) activity. Total protein concentration was measured using the BAC Protein Assay Reagent Kit (Pierce, Rockford, IL). MPO activity was measured using the method of o-dianisidine dihydrochloride oxidation.[19] MPO activity was expressed as the change in optical density (ΔOD) per min and per mL of BALF. W/D, total protein concentration in BALF, and MPO activity in BALF were used to determine histochemical lung injury.

Statistical analyses

All data are expressed as the mean ± standard deviation. Prism® ver. 4 (GraphPad Software, San Diego, CA) software was used for statistical calculations and figure preparations. Data were compared using Welch's t-test; p-values < 0.05 were considered to be statistically significant.

Results

Peak airway pressure and mean airway pressure

Figure 4 shows pPaw and mPaw at baseline and after 60 min ventilation. The pPaw in the IRV group was significantly increased after 60 min ventilation ($p < 0.05$). A statistically significant difference in pPaw after 60 min ventilation was also observed between the two groups ($p < 0.05$). In contrast, pPaw scarcely changed in the MBV group after 60 min ventilation ($p = 0.93$). No significant differences in mPaw were observed between the two groups either at baseline ($p = 0.27$) or after 60 min ventilation ($p = 0.40$).

PV curve

The pulmonary PV curves of both groups at baseline and after 60 min ventilation are shown in Fig. 5, in which the pressure is expressed as the average value for the corresponding volume, since no significant differences in pressure values were detected between the two groups. In comparison to the PV curves of the MBV group, those of the IRV group were slightly shifted towards higher pressures.

W/D and BALF analysis

W/D, total protein concentration in the BALF, and MPO activity in the BALF are presented in Fig. 6. A statistically significant difference between the two groups was determined for W/D (IRV: 7.50 ± 0.47;

MBV: 6.86 ± 0.18; $p < 0.05$). However, no significant differences were found in total protein concentration (IRV: 66.5 ± 30.2 μg/mL; MBV: 45.8 ± 32.2 μg/mL; $p = 0.24$) or MPO activity (IRV: 0.56 ± 0.10 ΔOD/mL/min; MBV: 0.42 ± 0.19 ΔOD/mL/min; $p = 0.12$).

Discussion

Many marathon runners have adopted the 2:2 breathing rhythm. We manufactured an intermittent positive pressure ventilation system that mimics the breathing rhythm of marathon runners. The lung-protective effect of the MBV on the pulmonary pre-edema model was examined using an isolated perfused rabbit lung. Compared to the IRV group, the MBV group had lower pPaw and W/D after 60 min ventilation, and the MBV was observed to have a preventive effect on the exacerbation of pulmonary edema.

Since the publication of the 2000 ARDS Network trial,[20] the focus of mechanical ventilation in acute respiratory failure has shifted from normalization of arterial blood gas values to lung protection. In recent years, low TV ventilation has secured a leading position among lung-protective ventilation strategies;[6] additionally, HFOV[8] and IRV[7] are also listed as possible options.

Low TV ventilation has a serious disadvantage since it sometimes causes respiratory acidosis at a pH < 7.2.[6] In a piglet model of VILI, it was found that even with low TV ventilation, high RR values activate transforming growth factor β pathways and exacerbate pulmonary edema.[21]

In HFOV, lung volume is secured by the mPaw. If the mPaw setting is too low, the lung volume decreases, and sufficient oxygenation cannot be obtained; in contrast, setting the mPaw too high can result in decreased cardiac output and increased pulmonary vascular resistance.[22] In the OSCILLATE trial,[8] a randomized control trial for ARDS, HFOV did not prove to be superior to low TV ventilation. In the same trial, the high mortality rate found for ARDS patients with HFOV was caused by circulatory suppression due to a high mPaw.[23] Moreover, when CO_2 is retained under HFOV, the only possible strategy is to decrease the frequency and increase the TV.[24]

In the IRV, pPaw values are kept low, but the mPaw is maintained at high values.[25] The improved oxygenation capacity of the IRV is attributed to the increase in mPaw[24] and the occurrence of intrinsic PEEP[26] due to the decrease in expiratory time. However, in mouse experiments with high TV ventilation, lung injury was induced more with the IRV than by conventional mechanical ventilation.[27]

During intense exercise, the O_2 demand increases beyond the limit of pulmonary diffusion capacity, thus increasing the alveolar-arterial oxygen difference and inducing hypoxemia.[28] It was shown that the heart rate increases to 145–180/min during a marathon.[29] In an exercise that corresponds to 80% of the maximum oxygen uptake rate, the mean pulmonary artery pressure increases up to 38 mmHg in young people, while the left atrial pressure increases up to 25 mmHg.[30] Subclinical interstitial pulmonary edema

is found in 17% of runners after a marathon.[31] The fact that the 2:2 breathing rhythm is favored empirically in situations such as a marathon, which has a long exercise load, suggests that this respiratory technique works effectively to prevent further progression of hypoxia and pulmonary edema. Moreover, the fact that the end-tidal CO_2 is not retained during a marathon, along with the increased metabolism over a long time,[13] suggests that the 2:2 breathing rhythm provides a sufficient capacity for CO_2 elimination.

In this current study, MBV ameliorated the progression of pulmonary edema in a pre-edema model. We suggest that alveolar overdistension was prevented in the MBV because the total ventilation volume for one respiratory cycle was divided into two fractions. In high TV ventilation of the isolated perfused rat lung, active sodium transport and Na-K-ATPase activity of the alveolar epithelium are impaired, and lung edema clearance is reduced.[32]

The isolated perfused rabbit lung model allowed the investigation of the effects of ventilatory strategies on the lungs without the influence of confounding factors, for example, the metabolization of inflammatory mediators by other organ systems. It is a reliable model by which lungs can be investigated under various pathophysiological conditions and it represents an accepted model in the study of VILI-related problems.[33-37]

The PV curves at the end of the experiment were not very different between the MBV and IRV groups. The pulmonary pre-edema model we employed can be considered as an early stage of lung injury, since no changes are observed in lung mechanics at early stages of lung injury, and lung mechanics are not a valid marker for early-stage lung injury.[38]

In small animals, acute extreme lung stretching rapidly develops into an increased permeability lung edema. The mechanism is thought to involve the destruction of vascular endothelial cells, which induces direct contact between the basement membrane and polymorphonuclear cells, rather than involving the recruitment of inflammatory cells.[2] In this study, there was no significant difference in MPO activity in the BALF between the MBV and IRV, suggesting that polymorphonuclear cells had not yet infiltrated into the alveolus.

Some limitations of the study include the following factors. The average frequency of steps taken during a marathon is about 180 per minute.[39] In the 2:2 breathing rhythm, the average RR during a marathon is 45 cycles/min, given that one cycle consists of a 1st inspiratory period, 2nd inspiratory period, 1st expiratory period, and 2nd expiratory period. The resting RR in humans is 12–20 breaths/min, whereas in rabbits, it is 32–60 breaths/min.[40] In the current study, we examined the effects of MBV with RRs of approximately 30 cycles/min in rabbits. Higher RRs should also be examined. In addition, future studies need to examine the effects of long-term MBV on O_2 uptake and CO_2 elimination in diseased lungs.

The 2:2 breathing rhythm in a marathon differs significantly from that in MBV because the former is a spontaneous ventilation, whereas the latter is an intermittent positive pressure ventilation. Thus, before the MBV approach can be applied in the clinic, its effects must be examined in larger animals that have breathing cycle values that are closer to those in humans during a marathon. In addition, MBV implementation requires the administration of sedatives or muscle relaxants, which needs to be taken into consideration prior to clinical use of the MBV. In severe ARDS with high airway pressure, if spontaneous breathing is preserved, transpulmonary pressure becomes too high, which can increase lung damage. Therefore, in severe ARDS, muscle relaxation may reduce lung damage.[41] Among the recent treatment strategies for ARDS, administration of muscle relaxants has been introduced as a treatment that may be tried for ARDS patients with a PaO_2/F_IO_2 ratio <150 mmHg.[42]

In conclusion, we successfully developed a prototype ventilator that can perform intermittent positive pressure ventilation, mimicking the breathing cycle of the 2:2 breathing rhythm. This mode of ventilation was named the “marathoners’ breathing rhythm ventilation”. The pPaw and W/D after 60 min ventilation were significantly lower in the MBV group than in the IRV group. Future studies could examine the lung protective effect of long-term MBV on diseased lungs in large animals.

Declarations

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The authors declare no conflict of interest.

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Abbreviations

ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; ΔOD, change in optical density; HFOV, high-frequency oscillatory ventilation; I:E, inspiratory:expiratory; IRV, inversed ratio ventilation; MBV, marathoners' breathing rhythm ventilation; mPaw, mean airway pressure; MPO, myeloperoxidase; PEEP, positive end-expiratory pressure; pPaw, peak airway pressure; PV, pressure volume; RR, respiratory rate; TV, tidal volume; VILI, ventilator-induced lung injury; W/D, lung wet-to-dry ratio

Figures

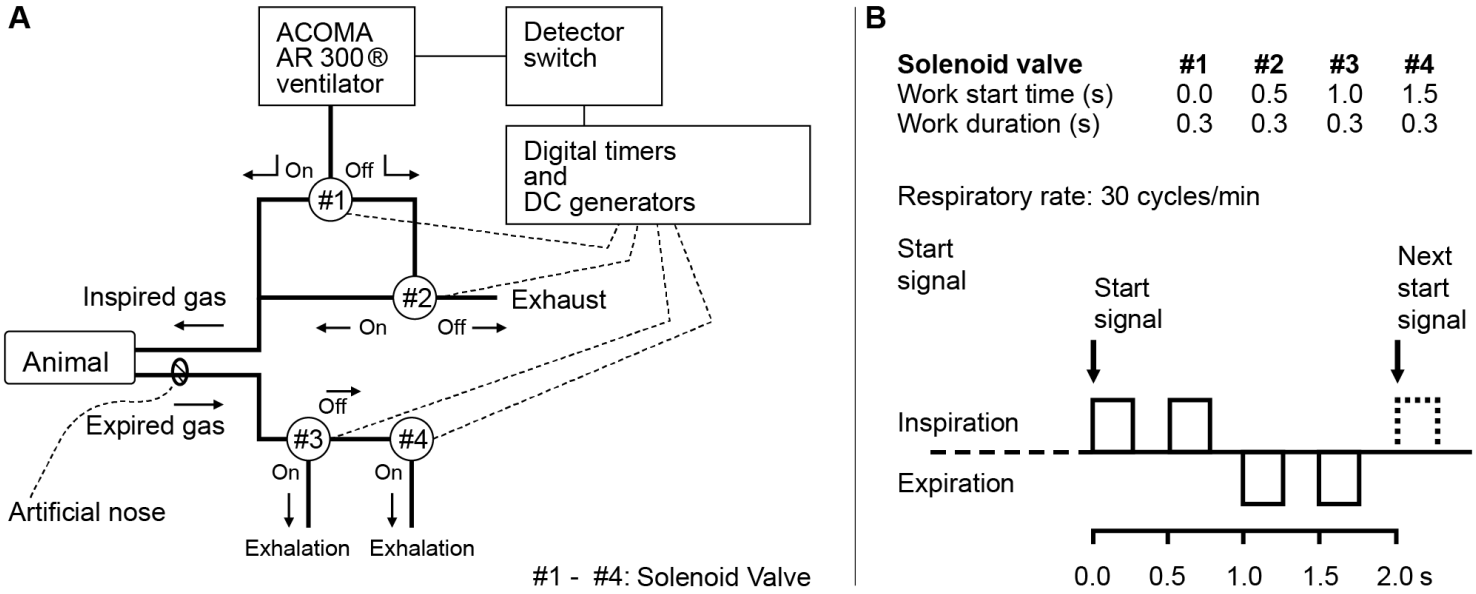

Figure 1

Schematic diagram of the prototype ventilator (A). Example of the time allocation for the four solenoid valves, with the respiration rate set to 30 cycles/min (B). In the MBV method, the 1st inspiratory, 2nd inspiratory, 1st expiratory, and 2nd expiratory phases taken together, are defined as one cycle.

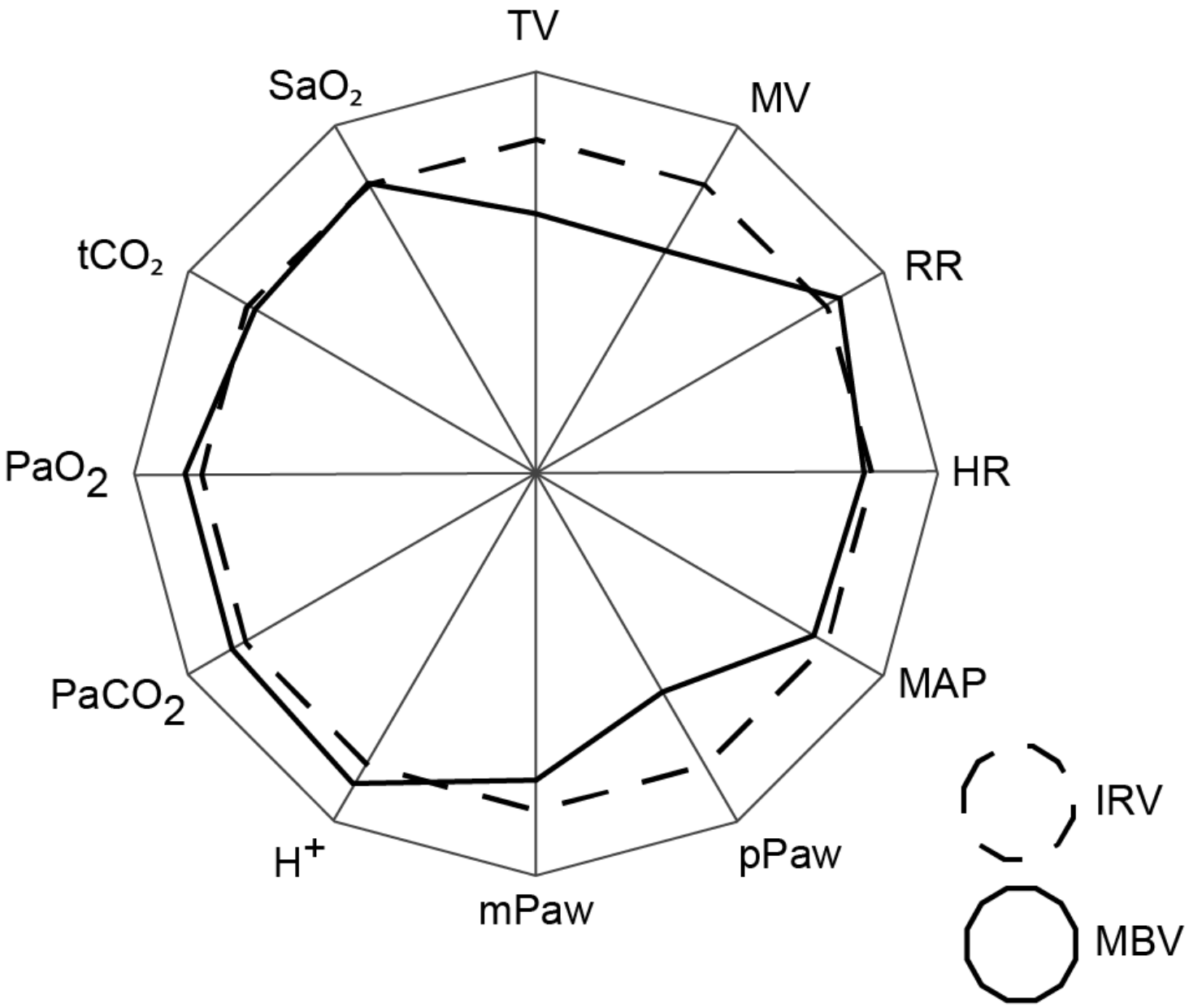

Figure 2

Radar chart of physiological parameters in the MBV method normalized with each value in the IRV method. The pH is expressed by the hydrogen ion concentration. H+, hydrogen ion concentration; HR, heart rate; MAP, mean arterial pressure; MV, minute volume; tCO2, total CO2 content

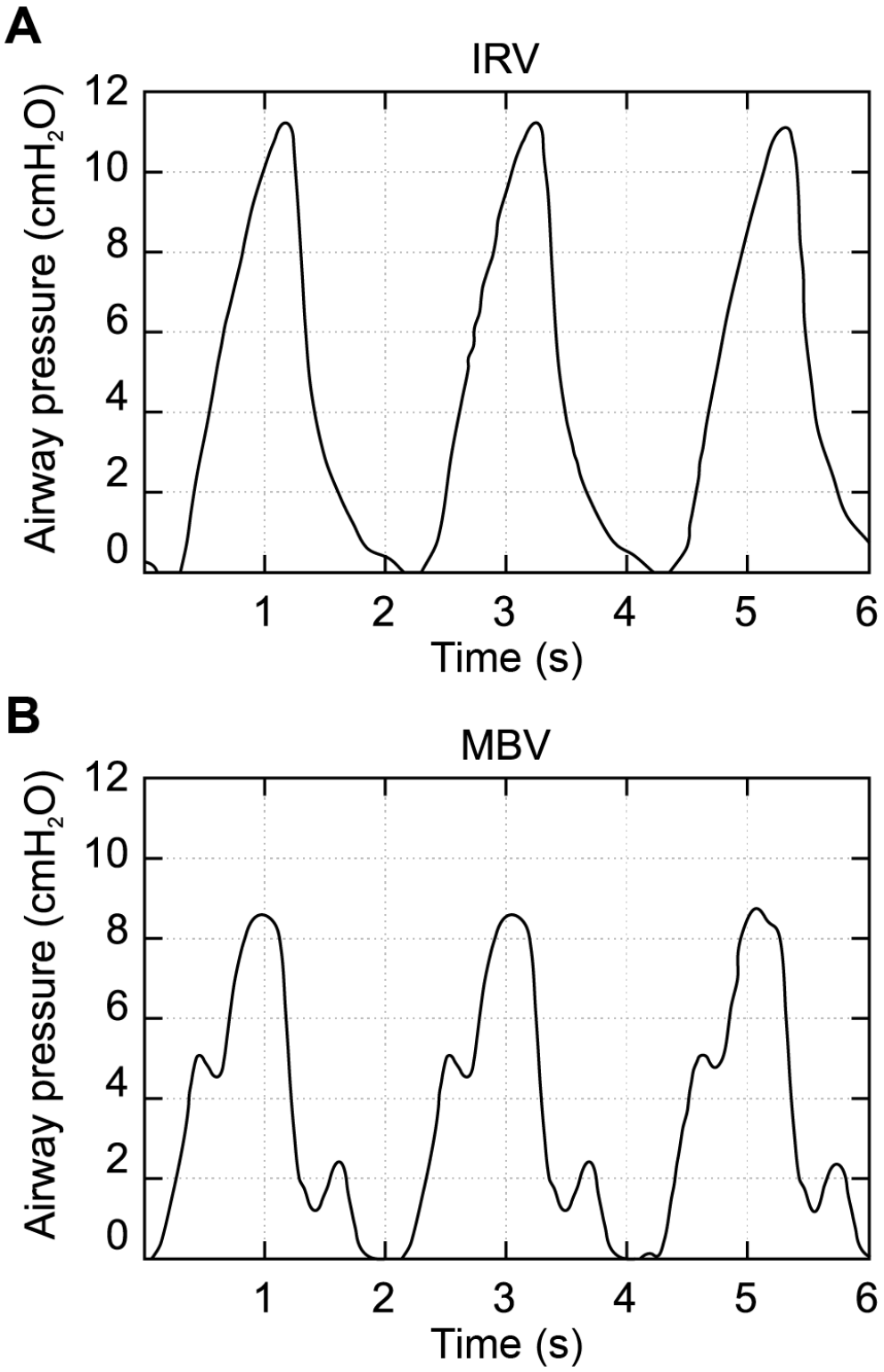

Figure 3

Typical waveforms of the airway pressure for the IRV (A) and MBV (B) methods in the same rabbit. In the MBV method, the airway pressure transiently decreases immediately after the end of the 1st inspiratory period and transiently increases immediately after the end of the 1st expiratory period.

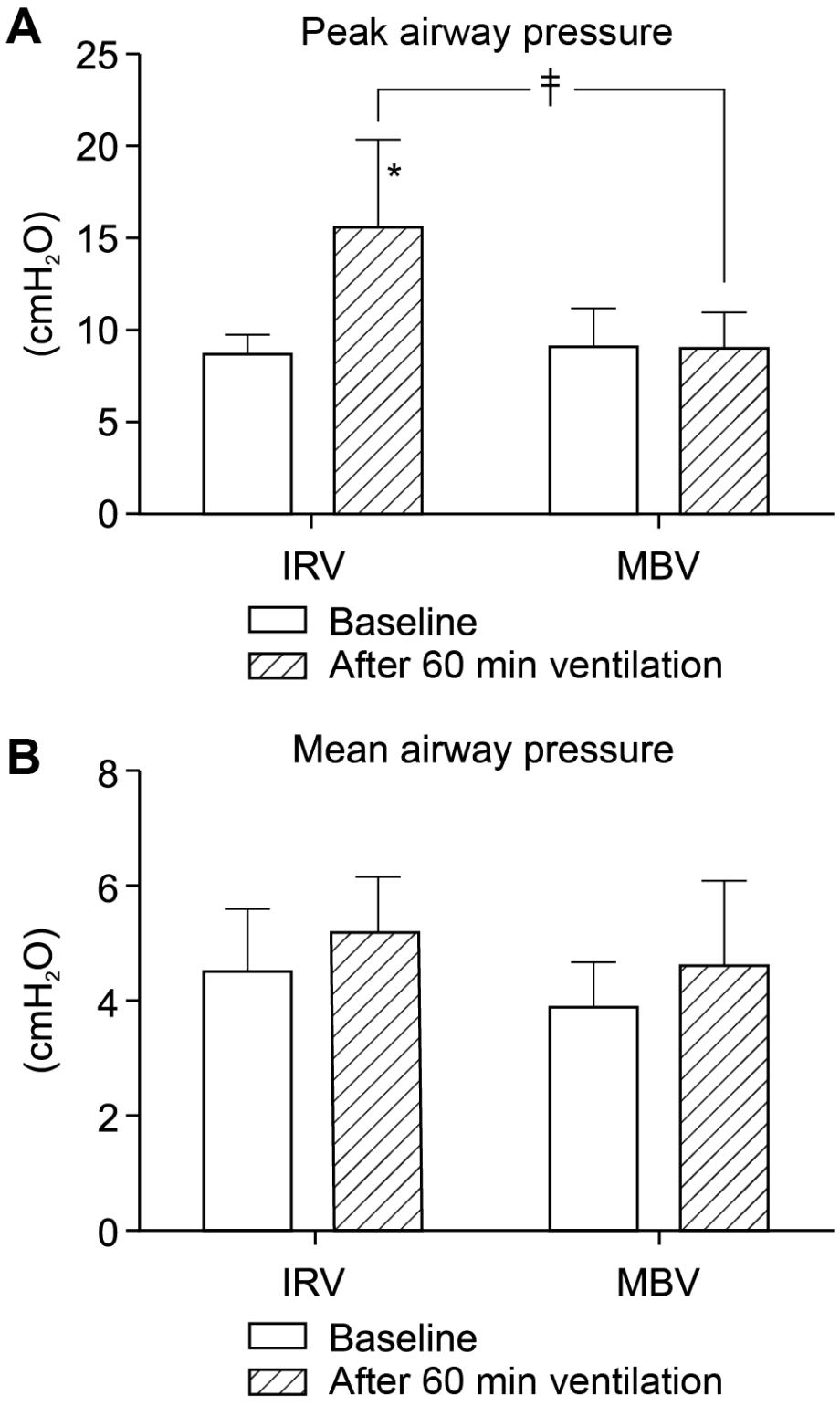

Figure 4

Changes in peak airway pressure (A) and mean airway pressure (B) in the IRV and MBV groups. The peak airway pressure significantly increases after 60 min ventilation in the IRV group (*$p < 0.05$). A significant difference is observed in the peak airway pressure after 60 min ventilation between the two groups (†$p < 0.05$).

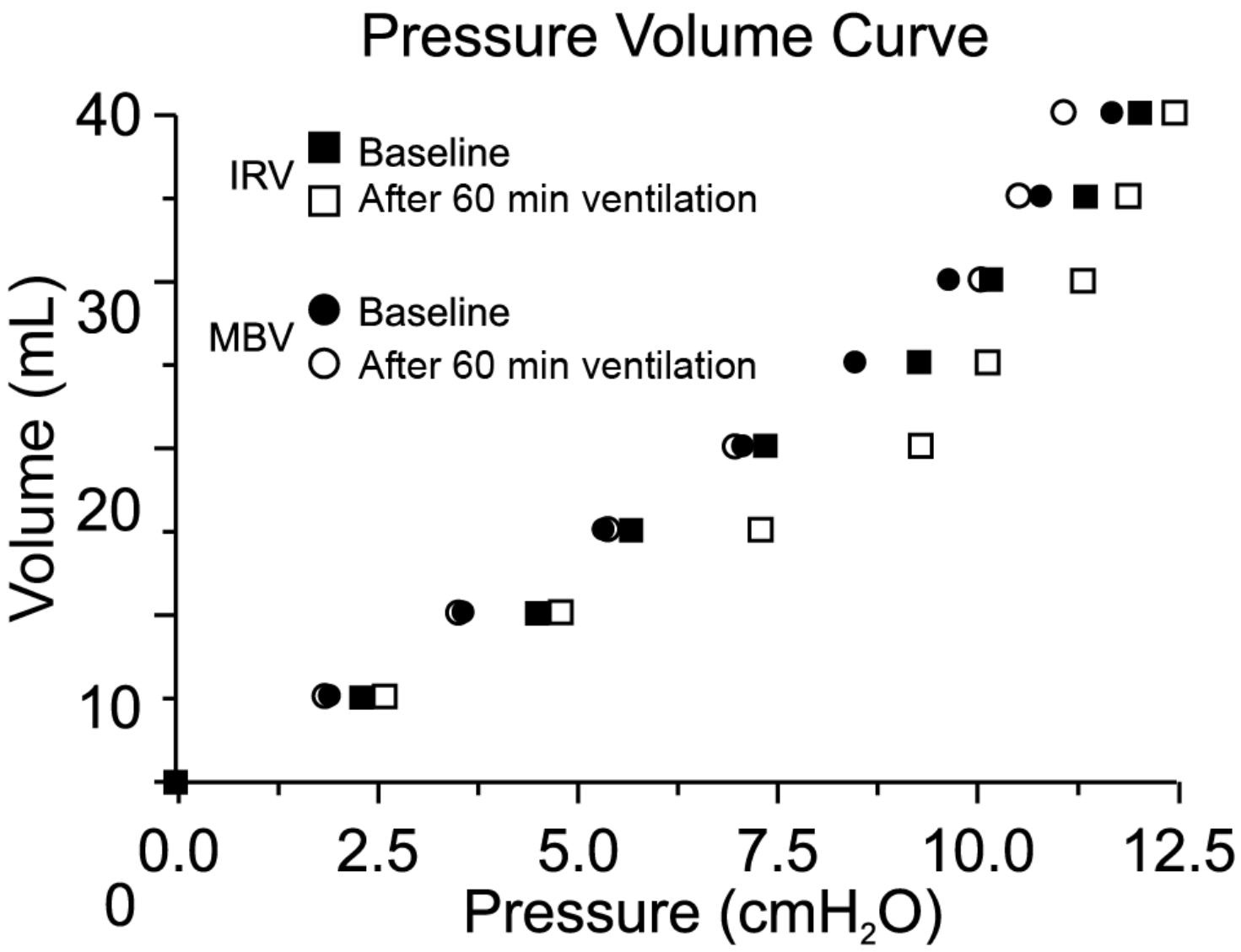

Figure 5

Pulmonary PV curves at baseline and 60 min after ventilation in the IRV and MBV groups. Pressure is expressed by the average value against each volume, since no significant differences are observed between groups at each pressure. Compared with the PV curves in the MBV group, the curves in the IRV group have shifted slightly to the higher pressure.

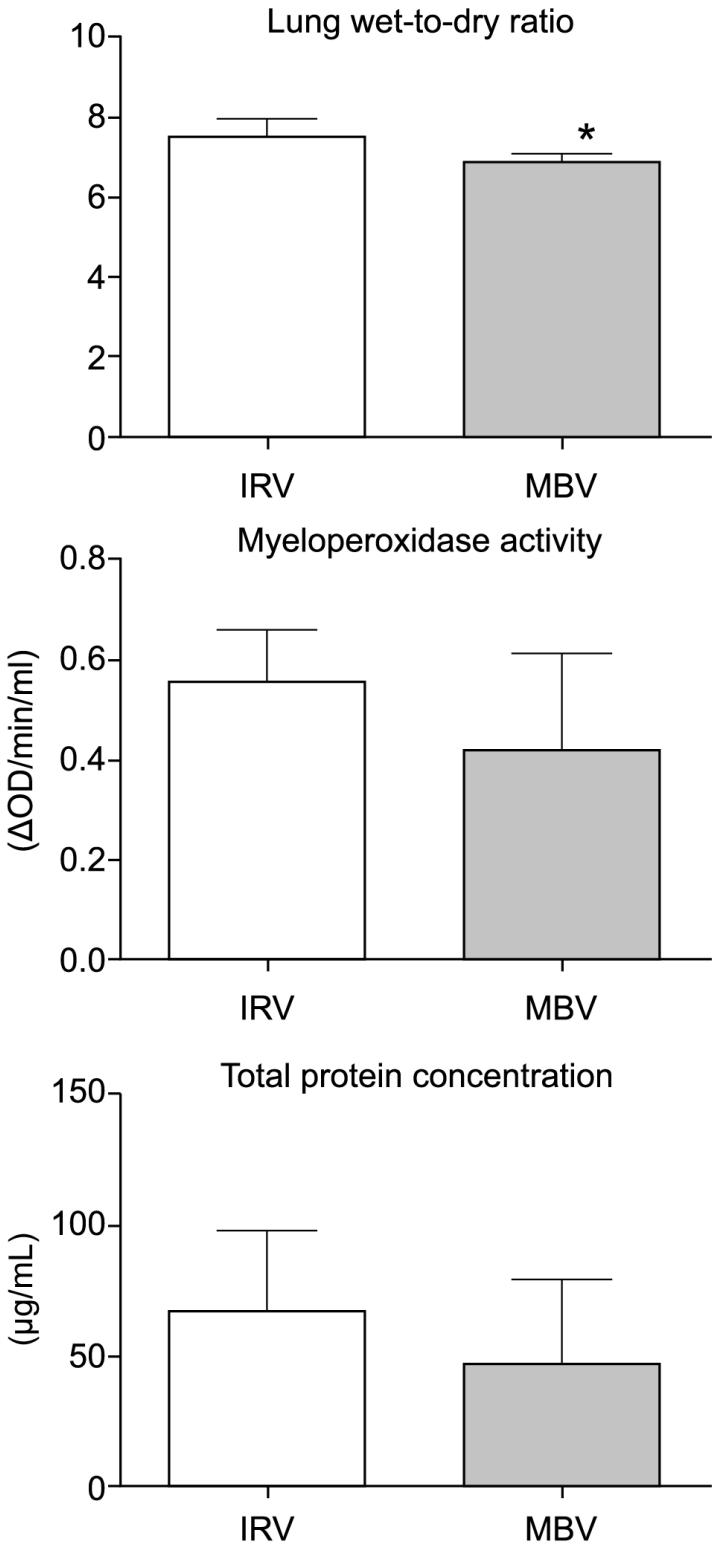

Figure 6

Comparison of lung wet-to-dry ratio and myeloperoxidase activity and total protein concentration between the IRV and MBV groups. A significant difference was observed in the lung wet-to-dry ratio between the two groups (*$p < 0.05$). ΔOD, change in optical density