Yonago Acta Medica 2021;64(2):229–233 doi: 10.33160/yam.2021.05.012

Prone Position Impairs Oxygen Supply-Demand Balance During Systemic Hypoxia in Rabbits

Yoshiaki Oshima,*† Naoto Okazaki,* Kazumi Funaki,* Shunsaku Takahashi,*‡ Tomomi Harada,*§ Akihiro Otsuki* and Yoshimi Inagaki*

**Division of Anesthesiology and Critical Care Medicine, Department of Surgery, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8504, Japan, †Department of Anesthesiology, Yonago Medical Center, Yonago 683-0006, Japan, ‡Department of Anesthesiology, Tottori Prefectural Central Hospital, Tottori 680-0901, Japan, and §Department of Anesthesiology, Ehime Prefectural Central Hospital, Matsuyama 790-0024, Japan*

ABSTRACT

Ventilation in the prone position improves the prognosis of patients with severe acute respiratory distress syndrome (ARDS). Contraindications to ventilation in this position include unstable systemic circulation. Only a few reports exist on the effects of prone ventilation in respiratory failure on systemic circulation. This animal study compared systemic hemodynamic changes between supine and prone positions in anesthetized rabbits under acute systemic hypoxia (breathing 15% O_2). Cardiac output and the systemic O_2 extraction ratio increased under the hypoxia, but only in the supine group. Besides, the rate pressure product was higher in the prone group than in the supine group. This study showed that prone ventilation increases myocardial O_2 consumption and suppresses compensatory mechanisms to maintain aerobic metabolism during systemic hypoxia. First of all, it will be necessary to examine the effect of prone ventilation on the O_2 supply-demand balance in the ARDS model.

Key words hypoxia; oxygen consumption; prone position; respiratory distress syndrome

In 1974, Bryan first proposed that the prone position effectively improves oxygenation in acute respiratory failure because it improves regional ventilation in the dorsal lung and reduces atelectasis.[1] A multicenter study in France showed that starting ventilation in the prone position early in the course of severe acute respiratory distress syndrome (ARDS) and continuing for 16 hours in combination with low tidal volume ventilation and the use of muscle relaxants markedly improved the prognosis of these patients.[2]

Contraindications to prone ventilation include cases with an unstable systemic circulation.[2] In severe ARDS, systemic circulation is rather unstable.[3] Only a few studies have examined the effect of ventilation in the prone position for ARDS on systemic circulation.[4] In ARDS patients with preload reserve, the prone position reduces right ventricular afterload by improving oxygenation and increasing cardiac output (CO).[4] To further improve the prognosis of severe ARDS, it is essential to investigate the effect of prone ventilation on systemic circulation. In an experiment with healthy adult volunteers under conscious and spontaneous breathing, the lateral position decreased myocardial O_2 consumption by reducing gravitational stress, resulting in a decrease in the O_2 consumption of the body as a whole.[5] Prone ventilation may also alter the O_2 supply-demand balance.

Severe ARDS is caused by a variety of factors and has a complex pathogenesis that can lead to systemic hypoxemia if not properly managed.[3] In this short communication, as a preliminary study, we examined the effect of prone position on the systemic circulation in a simple experimental model in which systemic hypoxemia was induced by inhalation of a low concentration of O_2. We presented the O_2 supply-demand balance in the prone position in anesthetized rabbits under acute systemic hypoxia (breathing 15% O_2).

MATERIALS AND METHODS

This protocol was approved by the Laboratory Animal Care Committee of the Faculty of Medicine at Tottori University (approval number 08-Y-59).

Experimental setting

Adult male Japanese white rabbits were anesthetized with 30 mg/kg pentobarbital administered via the ear vein and placed in the supine position. After local anesthesia of the anterior neck region with 1% lidocaine, the rabbits were tracheotomized and ventilated with

Corresponding author: Yoshiaki Oshima, MD, PhD
yoshimatomo@gmail.com
Received 2021 March 23
Accepted 2021 April 14
Online published 2021 May 2
Abbreviations: ARDS, acute respiratory distress syndrome; CO, cardiac output; DO_2, O_2 delivery; HR, heart rate; mAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; O_2ER, O_2 extraction ratio; PEEP, positive end-expiratory pressure; RPP, rate pressure product

air using a Harvard Rodent Ventilator 683 (Harvard Apparatus, Holliston, MA). The positive end-expiratory pressure (PEEP) was set to 3 cmH_2O and the tidal volume to 6 ml/kg. The respiratory rate was adjusted so that the $PaCO_2$ value was in the normal range. Pentobarbital (10 mg/kg/h), pancuronium bromide (3 mg/kg/h), and lactated Ringer's solution (10 ml/kg/h) were administered continuously via the ear vein.[6, 7]

CO was measured using the thermodilution technique. A 22 G catheter was placed into the right femoral artery. Another catheter (PE-50) was inserted through the right external jugular vein into the pulmonary artery and used to inject a bolus of 0.5 ml of saline at 5 °C. A 20 G catheter, with a built-in check valve to prevent blood leakage from the catheter hub (Supercath 5, Medikit, Tokyo, Japan), was inserted into the left external carotid artery. Through this catheter, a thermocouple probe (MLT1405, AD Instruments, Sydney, Australia) was implanted at the base of the aorta. The probe was connected with a Cardiac Output Pod ML313 (AD Instruments, Sydney, Australia) to monitor body temperature and CO. The blood gas was analyzed with iSTAT 200 (iSTAT Corp., East Windsor, NJ)

A preliminary experiment investigated the level of inhaled O_2 required to induce acute systemic hypoxia. Rabbit survival was examined while low concentrations of O_2 were administered. At 10% O_2, four animals died consecutively within 6 hours; at 15% O_2, no animals died within 6 hours, but some animals died after 9 hours. In this study, 15% O_2 was thus administered, and the animals were monitored for 6 hours.

Experimental protocol

We studied 18 rabbits (body weight, 2.2–2.7 kg) equally randomized to the prone (9) and supine (9) positions, respectively. Thirty minutes after the end of the surgical procedures, animals in the prone group were changed from the supine to the prone position. The position of the supine group was not changed from the onset of the surgical procedure. The inhaled gas was then switched to 15% O_2 in balance N_2 in both groups, and systemic hemodynamic changes were measured for 6 hours. In the prone position, rabbits were placed on a handmade styrofoam table that was hollowed out where the anterior chest and abdomen rested. In both groups, a small-animal warmer/thermometer system (BWT-100, Bio Research Center, Nagoya, Japan) was placed under the rabbit's trunk to control the blood temperature at the base of the aorta to 38–39 °C. In both groups, CO measurements were made while breathing room air (baseline) and after 1.5, 3.0, 4.5, and 6.0 hours of hypoxia. Blood gas analysis was also performed at each interval, except for the 4.5-hour measurement.

Statistical analysis

All data are expressed as the mean ± SE. GraphPad Prism ver. 4 software (GraphPad Software, San Diego, CA) was used for statistical analysis. Two-way ANOVA was used for between-group comparisons and one-way ANOVA for within-group comparisons. Bonferroni's test was used for both post hoc tests. Statistical significance was accepted at $P < 0.05$.

RESULTS

In both groups, the PaO_2 at 1.5, 3.0, and 6.0 hours of hypoxia was significantly lower than the baseline value (Fig. 1A). In both groups, the mean arterial pressure at 6.0 hours of hypoxia was significantly lower than the baseline value (Fig. 1B). The heart rates (HR) at 1.5, 3.0, and 4.5 hours of hypoxia were 262.8 ± 10.4, 264.5 ± 10.4, and 265.8 ± 11.4 (beats/min) in the prone group, and 240.6 ± 7.3, 238.5 ± 8.9, and 241.1 ± 9.9 (beats/min) in the supine group, respectively. The HR at 1.5, 3.0, and 4.5 hours of hypoxia was significantly higher in the prone group than in the supine group. The rate pressure product (RPP) at 1.5, 3.0, and 4.5 hours of hypoxia was significantly higher in the prone group than in the supine group (Fig. 1C). At all measurement times, the mean pulmonary arterial pressure was not significantly different between the two groups (Fig. 1D). In the supine group, the CO at 4.5 and 6.0 hours of hypoxia was significantly higher than the baseline value (Fig. 1E). In both groups, the O_2 delivery at 1.5, 3.0, and 6.0 hours of hypoxia was significantly lower than the baseline value (Fig. 1F). In the supine group, the systemic O_2 extraction ratio (O_2ER) at 1.5, 3.0, and 6.0 hours of hypoxia was significantly higher than the baseline value (Fig. 1G).

DISCUSSION

This study compared changes in the systemic circulation between supine and prone positions in anesthetized rabbits under systemic hypoxia. Notable differences were that CO and the systemic O_2ER increased during the hypoxia in the supine group but not in the prone group. Besides, RPP was higher in the prone group than in the supine group.

During systemic hypoxia, several compensatory mechanisms maintain aerobic metabolism. These include an increase in HR and CO via medullary and peripheral chemoreceptors,[8] redistributions of blood flow to vital organs, and an increase in O_2 extraction ability.[9–13] Because the prone position decreases venous return due to compression of the inferior vena cava,[14]

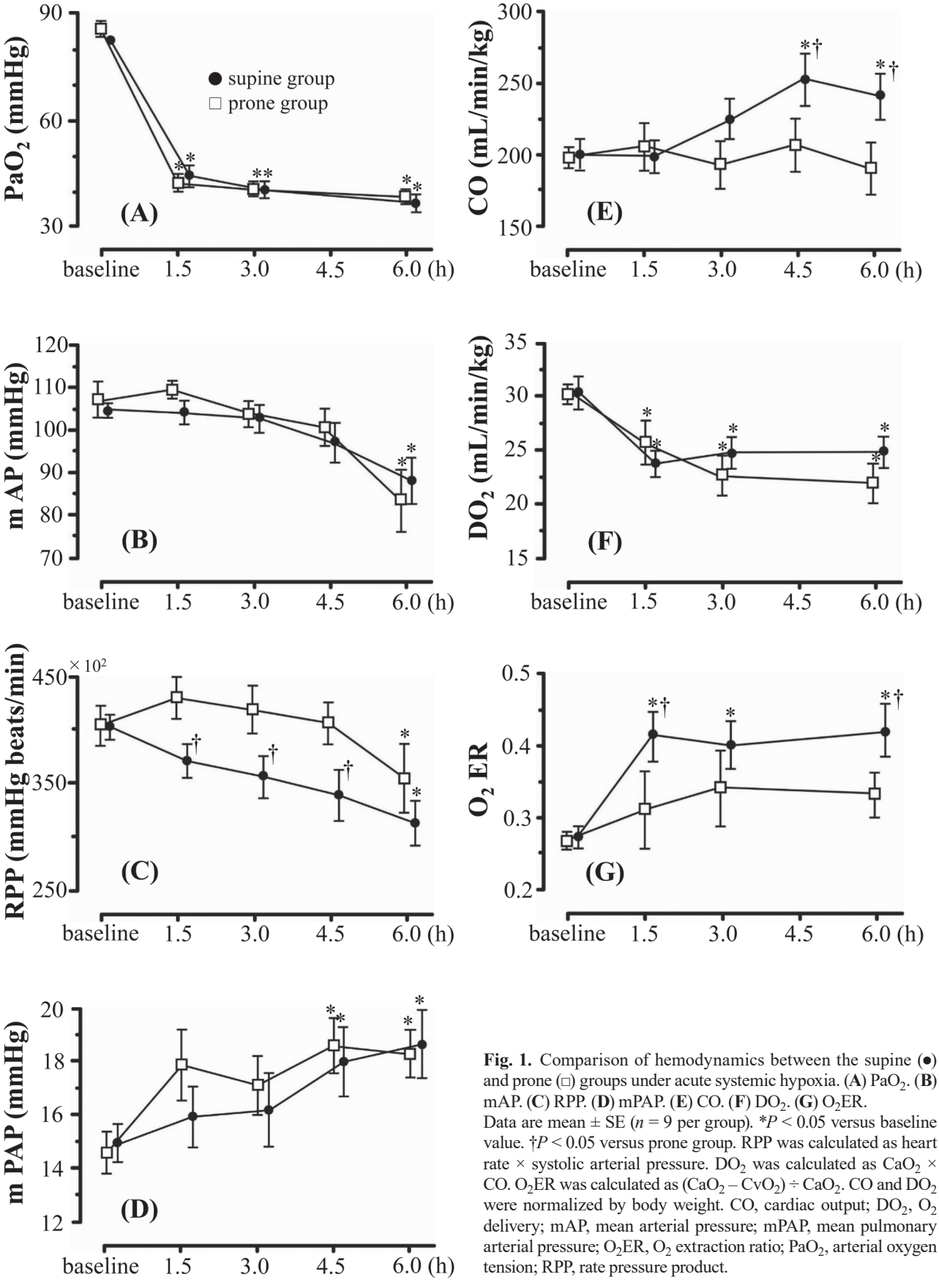

Fig. 1. Comparison of hemodynamics between the supine (●) and prone (□) groups under acute systemic hypoxia. (**A**) PaO_2. (**B**) mAP. (**C**) RPP. (**D**) mPAP. (**E**) CO. (**F**) DO_2. (**G**) O_2ER.
Data are mean ± SE (n = 9 per group). *P < 0.05 versus baseline value. †P < 0.05 versus prone group. RPP was calculated as heart rate × systolic arterial pressure. DO_2 was calculated as CaO_2 × CO. O_2ER was calculated as $(CaO_2 - CvO_2) \div CaO_2$. CO and DO_2 were normalized by body weight. CO, cardiac output; DO_2, O_2 delivery; mAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; O_2ER, O_2 extraction ratio; PaO_2, arterial oxygen tension; RPP, rate pressure product.

the CO may not have increased even with systemic hypoxia in the prone group in this study. The redistribution of blood flow from the abdominal organs to the heart and brain results in the transfer of blood flow from organs with a low O_2 extraction ability to organs with a high O_2 extraction ability, thus increasing the O_2 extraction ability of the body as a whole.[15, 16] Systemic O_2ER is the sum of the O_2ER of all tissues, and the ratio at rest is 0.25–0.35.[17] In anesthetized dogs with acute systemic hypoxia, phenoxybenzamine, an alpha-adrenergic blocker, reduced systemic O_2ER from 0.87 to 0.46 by inhibiting redistribution of blood flow, and consequently impaired aerobic metabolism.[18] In this study, the fact that systemic O_2ER in the prone position did not increase under systemic hypoxia may suggest an impaired redistribution of blood flow to vital organs. However, further studies are required to confirm this mechanism.

RPP correlates with myocardial O_2 consumption.[19, 20] Under spontaneous breathing in healthy human adults, the lateral position decreased myocardial O_2 consumption via reduction of gravitational stress.[5] In this study, the RPP was greater in the prone position because the HR, not the arterial pressure, was greater in the prone position. Compared to the supine position, the prone position was more deleterious in the balance of myocardial O2 supply and demand. In patients under general anesthesia, the prone position itself has been reported to slightly increase HR compared to the supine position.[14]

This study showed that prone ventilation increases myocardial O_2 consumption and suppresses compensatory mechanisms to maintain aerobic metabolism during systemic hypoxia. In ARDS, systemic hypoxia as in this study can be avoided by increasing the inspired O_2 concentration or applying PEEP. Therefore, there are difficulties in applying the results of this study to ARDS. However, in endotoxemia, even if the O_2 supply is maintained at a high level, the prognosis is not improved because the ability of O_2 uptake at the organ or cellular level is impaired.[21] First of all, it will be necessary to examine the effect of prone ventilation on the O_2 supply-demand balance in the ARDS model.

Acknowledgments: We would like to thank Motomu Nada for creating figures, Kyoko Nakada for assistance in gathering references. This work was supported in part by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science, and Technology (No. 20591830).

The authors declare no conflict of interest.

REFERENCES

1 Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. Am Rev Respir Dis. 1974;110:143-4. PMID: 4440945
2 Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159-68. DOI: 10.1056/NEJMoa1214103, PMID: 23688302
3 Squara P, Dhainaut JFA, Artigas A, Carlet J. Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS Study. Intensive Care Med. 1998;24:1018-28. DOI: 10.1007/s001340050710, PMID: 9840234
4 Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2013;188:1428-33. DOI: 10.1164/rccm.201303-0593OC, PMID: 24102072
5 Jones AYM, Dean E. Body position change and its effect on hemodynamic and metabolic status. Heart Lung. 2004;33:281-90. DOI: 10.1016/j.hrtlng.2004.04.004, PMID: 15454907
6 Maeda Y, Fujino Y, Uchiyama A, Matsuura N, Mashimo T, Nishimura M. Effects of peak inspiratory flow on development of ventilator-induced lung injury in rabbits. Anesthesiology. 2004;101:722-8. DOI: 10.1097/00000542-200409000-00021, PMID: 15329597
7 Richard JC, Bregeon F, Costes N, Bars DLE, Tourvieille C, Lavenne F, et al. Effects of prone position and positive end-expiratory pressure on lung perfusion and ventilation. Crit Care Med. 2008;36:2373-80. DOI: 10.1097/CCM.0b013e31818094a9, PMID: 18596639
8 Eyzaguirre C, Fitzgerald R, Lahiri S, Zapata P. Arterial chemoreceptors. In: Shepherd J T, Abboud FM, Geiger SR, editors. Handbook of Physiology, Section 2, vol. 3, The Cardiovascular System. Bethesda: American Physiological Society; 1983. p. 557-621.
9 Walley KR, Becker CJ, Hogan RA, Teplinsky K, Wood LD. Progressive hypoxemia limits left ventricular oxygen consumption and contractility. Circ Res. 1988;63:849-59. DOI: 10.1161/01.RES.63.5.849, PMID: 3180352
10 McPherson RW, Zeger S, Traystman RJ. Relationship of somatosensory evoked potentials and cerebral oxygen consumption during hypoxic hypoxia in dogs. Stroke. 1986;17:30-6. DOI: 10.1161/01.STR.17.1.30, PMID: 3945980
11 Lutz J, Henrich H, Bauereisen E. Oxygen supply and uptake in the liver and the intestine. Pflugers Arch. 1975;360:7-15. DOI: 10.1007/BF00584322, PMID: 1237867
12 Hughes RL, Mathie RT, Campbell D, Fitch W. Systemic hypoxia and hyperoxia, and liver blood flow and oxygen consumption in the greyhound. Pflugers Arch. 1979;381:151-7. DOI: 10.1007/BF00582346, PMID: 574255
13 Gotshall RW, Miles DS, Sexson WR. Renal oxygen delivery and consumption during progressive hypoxemia in the anesthetized dog. Exp Biol Med. 1983;174:363-7. DOI: 10.3181/00379727-174-41749, PMID: 6420794
14 Edgcombe H, Carter K, Yarrow S. Anaesthesia in the prone position. Br J Anaesth. 2008;100:165-83. DOI: 10.1093/bja/aem380, PMID: 18211991
15 Krasney JA. Regional circulatory responses to arterial hypoxia in the anesthetized dog. American Journal of Physiology-Legacy Content. 1971;220:699-704. DOI: 10.1152/ajplegacy.1971.220.3.699, PMID: 5545679

16 Adachi H, Strauss W, Ochi H, Wagner HN Jr. The effect of hypoxia on the regional distribution of cardiac output in the dog. Circ Res. 1976;39:314-9. DOI: 10.1161/01.RES.39.3.314, PMID: 954160

17 Dantzker DR, Foresman B, Gutierrez G. Oxygen supply and utilization relationships. A reevaluation. Am Rev Respir Dis. 1991;143:675-9. DOI: 10.1164/ajrccm/143.3.675, PMID: 2001082

18 Cain SM. Effects of time and vasoconstrictor tone on O_2 extraction during hypoxic hypoxia. J Appl Physiol. 1978;45:219-24. DOI: 10.1152/jappl.1978.45.2.219, PMID: 681206

19 Aksentijević D, Lewis HR, Shattock MJ. Is rate-pressure product of any use in the isolated rat heart? Assessing cardiac 'effort' and oxygen consumption in the Langendorff-perfused heart. Exp Physiol. 2016;101:282-94. DOI: 10.1113/EP085380, PMID: 26585840

20 Kitamura K, Jorgensen CR, Gobel FL, Taylor HL, Wang Y. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol. 1972;32:516-22. DOI: 10.1152/jappl.1972.32.4.516, PMID: 5026501

21 Suetrong B, Walley KR. Lactic Acidosis in Sepsis: It's Not All Anaerobic. Chest. 2016;149:252-61. DOI: 10.1378/chest.15-1703, PMID: 26378980