

Inhaled Isoflurane for Life-Threatening Bronchospasm in Children

Seo Hee Yoon, MD, PhD,¹ Yoon Hee Kim, MD,^{1,*} In Suk Sol, MD,¹
Min Jung Kim, MD,¹ Hyo Sun Kim, MD,² Kyung Won Kim, MD, PhD,¹
Myung Hyun Sohn, MD, PhD,¹ and Chuhi Joo Lyu, MD, PhD²

In this study, we present 2 pediatric cases with different responses to inhaled isoflurane therapy for refractory life-threatening bronchospasm. Case 1, a 1-year-old boy with chronic lung disease of infancy was admitted with severe dyspnea and wheezing. Since he became unresponsive to conventional therapies, namely, nebulized albuterol and ipratropium bromide, intravenous corticosteroids, and magnesium with mechanical ventilation, inhalation of 1% isoflurane was initiated. After 2 h of isoflurane inhalation therapy, his respiratory acidosis resolved and he was successfully weaned. Case 2, a 5-year-old girl with bronchiolitis obliterans syndrome, following allogeneic peripheral stem cell transplantation for B cell acute lymphoblastic leukemia, was admitted after 1 day of sudden-onset dyspnea. Along with severe bronchospasm, her hypercapnia and high peak airway pressure did not improve with conventional therapies. Therefore, isoflurane was started at 1.5%, but discontinued within 1 h due to aggravation of hypercapnia. She was eventually placed on extracorporeal membrane oxygenation. These cases highlight that isoflurane inhalation could be lifesaving for those with refractory bronchospasm, but that it should be used carefully since the patient response can vary based on the underlying disease.

Keywords: bronchial spasm, inhalational anesthetics, child, isoflurane

Introduction

THE VOLATILE ANESTHETIC agent isoflurane is a halogenated ether that causes bronchodilation through a number of mechanisms.¹ Due to its ability to reduce respiratory resistance, it has been used to treat severe bronchospasm that is refractory to conventional therapies.^{2–4} Herein, we report 2 cases involving the use of isoflurane inhalation in children with severe, sudden-onset bronchospasm with different underlying diseases. This retrospective case review was approved by the Institutional Review Board of our institution (Severance Hospital, IRB number: 4-2017-1036).

Case Presentation

Case 1

A 1-year-old boy with a history of chronic lung disease (CLD) of infancy and chromosome 2p duplication syndrome

(2pD) was admitted 1 day after onset of fever and dyspnea. At presentation, he had severe chest wall retraction with oxygen saturation of 58% on room air. His vital signs were as follows: blood pressure (BP), 61/47 mmHg; pulse rate (PR), 109 beats/min; respiration rate (RR), 30 breaths/min; and body temperature (BT), 37.6°C. On auscultation, rales and wheezing sounds were heard over both lung fields. Initial arterial blood gas analysis (ABGA) values were as follows: pH, 7.22; partial pressure of arterial carbon dioxide (PaCO₂), 96 mmHg; PaO₂, 38 mmHg; and HCO₃⁻, 40.2 mmol/L. Laboratory test results were as follows: hemoglobin, 9.0 g/dL; C-reactive protein, 53.0 mg/L (reference range: 0–8 mg/L). Other laboratory findings were nonspecific. On comparison to a previous chest radiograph, bilateral perihilar consolidation and a right upper lobe collapse were noted (Fig. 1). Initial sputum and blood cultures were all negative.

He became refractory to repeated nebulized albuterol and budesonide with intravenous (IV) corticosteroids, and showed rapid deterioration requiring intubation and mechanical

¹Division of Pediatric Pulmonology and Pediatric Critical Care Medicine, Department of Pediatrics, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

²Division of Pediatric Hematology and Oncology, Department of Pediatrics, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

*Current affiliation: Division of Pediatric Pulmonology and Pediatric Critical Care Medicine, Department of Pediatrics, Gangnam Severance Hospital, Yonsei University College of Medicine, Gangnam-gu, Seoul, Korea.



FIG. 1. Chest radiograph showing bilateral perihilar consolidation and collapse of both upper lobes in Case 1. (A) Previous OPD routine checkup (B) at emergency room and (C) after intubation. OPD, outpatient department.

ventilation (Fig. 2A). The ventilator was set to synchronized intermittent mandatory ventilation mode and the settings were as follows: FiO_2 , 0.7; RR, 30 breaths/min; tidal volume (TV), 9 mL/kg; positive end-tidal pressure (PEEP), 5 mmHg. IV sedatives with muscle relaxant were administered for sedation and pain control during mechanical ventilation. Hypercapnia temporarily improved after applying mechanical ventilation. Then he was moved to the intensive care unit (ICU), and his breathing sounds were still markedly decreased. As the PaCO_2 worsened from 57 to 138 mmHg, continuous IV infusion of aminophylline, isoproterenol, and magnesium was administered for sustained bronchospasm. Ventilator mode was changed to pressure-regulated volume-control (PRVC) mode and settings were adjusted as follows: FiO_2 , 0.55–1.0; RR, 15–40 breaths/min; TV, 6–10 mL/kg; PEEP, 3–5 mmHg; I:E ratio 1:2 to 1:4. Nevertheless, despite these efforts, hypercapnia was sustained (Fig. 2).

Therefore, we decided to start inhalation isoflurane therapy at a concentration of 1% in the operating room. The

PaCO_2 level was monitored by ABGA. All sedative and muscle relaxant drugs were discontinued to prevent the potential development of hypotension.⁵ BP dropped within 5 min after inhalation initiation, but quickly recovered without any management. After 20 min of isoflurane inhalation, PaCO_2 steadily decreased and his breath sound became clear. Therefore, the concentration of inhaled isoflurane was tapered to 0.4%. After a total of 2 h and 10 min of isoflurane inhalation, respiratory acidosis and high peak inspiratory pressure (PIP) were improved and sustained stably. Thus, isoflurane treatment was discontinued without tapering the concentration.

We then tried weaning after tapering sedatives and muscle relaxant, however, the patient showed tachypnea and chest retraction and so the weaning trial failed. We suspect it was due to the development of ventilator-associated pneumonia (initial blood/sputum/urine cultures were all negative, but *Acinetobacter baumannii* was isolated in the sputum culture, which was collected after isoflurane inhalation therapy), and so, he was finally extubated 2 weeks later on improving his follow-up chest X-ray.

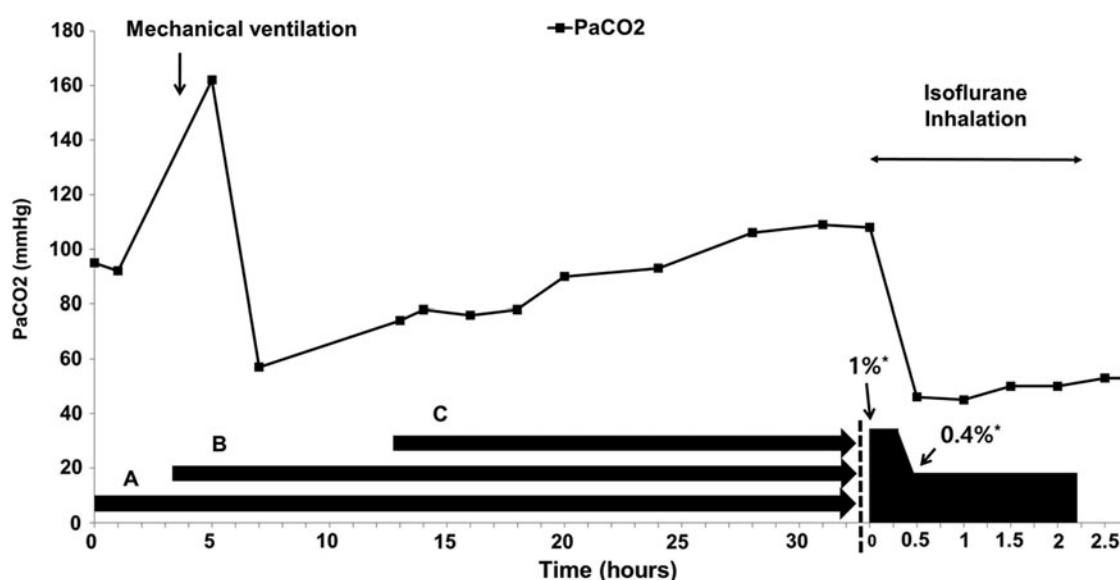


FIG. 2. Partial pressure of arterial carbon dioxide (PaCO_2) with management until and during isoflurane inhalation in Case 1 with A: nebulized albuterol and budesonide with IV corticosteroids; B: IV midazolam, ketamine, and fentanyl with muscle relaxant (atracurium); and C: continuous IV infusion of aminophylline and isoproterenol. *Isoflurane concentration. IV, intravenous.

Case 2

A 5-year-old girl with bronchiolitis obliterans syndrome (BOS) after allogeneic peripheral stem cell transplantation was admitted 1 day after the onset of cough and dyspnea. She had been diagnosed with B cell acute lymphoblastic leukemia 14 months prior, and had undergone unrelated peripheral blood stem cell transplantation (uPBSCT) 9 months before. Two months prior, she was diagnosed with BOS and started oral deflazacort and montelukast, inhaled salmeterol/fluticasone propionate, and albuterol (as needed) for the management of BOS. Treatment was successful for 2 months.

At admission, she had an oxygen saturation of 96% on room air. Her vital signs were as follows: BP, 113/88 mmHg; PR, 163 beats/min; BT, 36.8°C; and RR, 22 breaths/min. Her breath sounds were decreased on auscultation in the left lung field. A chest radiograph revealed hyperinflation in both lungs and new cavitory lesion in the left apex (Fig. 3B).

Initial special stains and cultures for bacteria and fungus from sputum and blood were all negative, whereas nontuberculosis mycobacterium was isolated from sputum after 1 month. She was started oxygen supplementation via nasal cannula and maintained her previous prescription for BOS.

However, on HOD (hospital day) 3, respiratory failure, with greatly diminished breath sounds on auscultation in both lung fields, was noted. ABGA results showed severe respiratory acidosis: pH, 7.19; PaCO₂, 87.8 mmHg; PaO₂, 71.8 mmHg; HCO₃⁻, 34.5 mmol/L. She was emergently intubated and received mechanical ventilation with the PRVC mode in the ICU. Ventilator settings were adjusted as follows: FiO₂, 0.4–0.8; TV, 6–7 mL/kg; RR, 15–30 breaths/min; PEEP, 3–5 mmHg. I:E ratio 1:2 to 1:3. Broad-spectrum antibiotics were started due to her immunosuppressed status. IV methylprednisolone, aminophylline, and magnesium were administered along with nebulized albuterol and ipratropium. Despite these therapies, hypercapnia and decreased breath sounds were sustained (Fig. 4). Since she had hypertension, we could not use isoproterenol.

We decided to initiate inhaled isoflurane therapy at 1% in the operating room. After 15 min of isoflurane inhalation, BP lowered from, systolic BP/diastolic BP, 165/90 to 125/60 mmHg, but lung sounds and high PIP showed no improvements. Therefore, isoflurane concentration was increased to 1.5% and we administered continuous IV norepinephrine during the therapy. BP was then sustained

within the normal range throughout the therapy; however, isoflurane had to be stopped due to the consistent increase in PaCO₂ from 69 to 139 mmHg within 1 h (Fig. 4).

The patient was eventually placed on extracorporeal membrane oxygenation (ECMO) the next day. Unfortunately, she could not be weaned from the ECMO, and died of uncontrolled bleeding after 4 weeks.

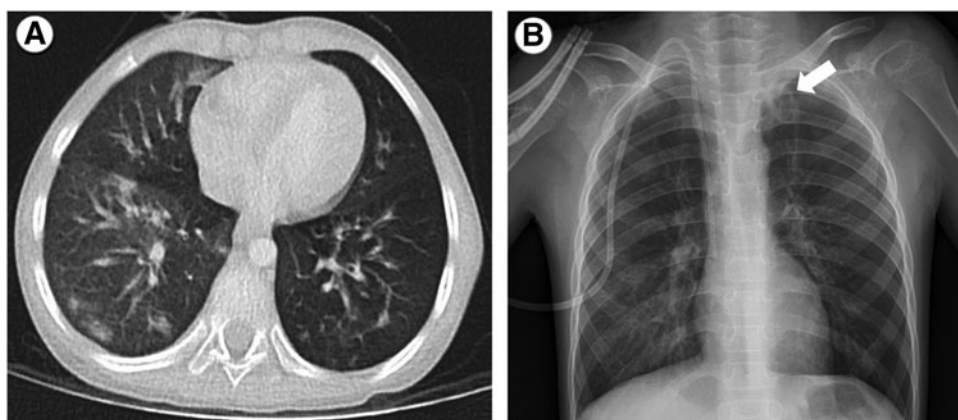
Discussion

The management of life-threatening bronchospasm is still a challenging issue. The conventional therapies of status asthmaticus include supplemental oxygen, short-acting beta2-agonists, inhalation of anticholinergics with systemic corticosteroids, and IV magnesium sulfate. Other rescue therapies include methylxanthines, DNase, ketamine, sodium bicarbonate, and heliox. More invasive therapeutic options in critical care setting include mechanical ventilation, inhalational anesthetics, and ECMO.⁶ However, applying mechanical ventilation to severe bronchospasm often results in the development of air leak or barotrauma.^{2,6} Moreover, ECMO requires specialized equipment with trained staff and also increases the risk of serious complications, such as bleeding or stroke.⁷

Inhalational anesthetics have been used in patients with status asthmaticus as rescue therapy for decades.⁸ The known mechanisms of action include direct relaxation of bronchial smooth muscle, stimulation of beta-adrenergic receptor, antagonism of histamine, and acetylcholine action.¹ Thus, anesthetics are expected to produce further bronchodilation after treatment with usual bronchodilators.

In the cases reported here, we administered inhaled isoflurane to 2 patients with severe bronchospasm, due to a specific underlying disease. The first case had CLD and 2pD, a very rare syndrome caused by the duplication of the short arm of chromosome 2, characterized by a prominent forehead, hypertelorism, and mental retardation. Respiratory complications are reported in many cases, mostly due to skeletal abnormalities of the thorax.^{9,10} The long-term morbidity of CLD includes pulmonary hypertension and airway hyperresponsiveness.¹¹ In this case, there were no skeletal abnormalities of the thorax, so infantile asthma complicating CLD was felt to be the main cause of respiratory failure. The patient showed rapid improvement of pH and PaCO₂ within 2 h of isoflurane initiation. This

FIG. 3. (A) Diffuse air trapping in both lungs with mild mosaic attenuation in the *right middle* and lower lobes seen in high-resolution computed tomography of the chest, which was taken 2 months before admission. (B) Chest radiograph showing hyperinflation in both lungs and the new cavitory lesions in the *left apex* of the lung (arrow) in Case 2.



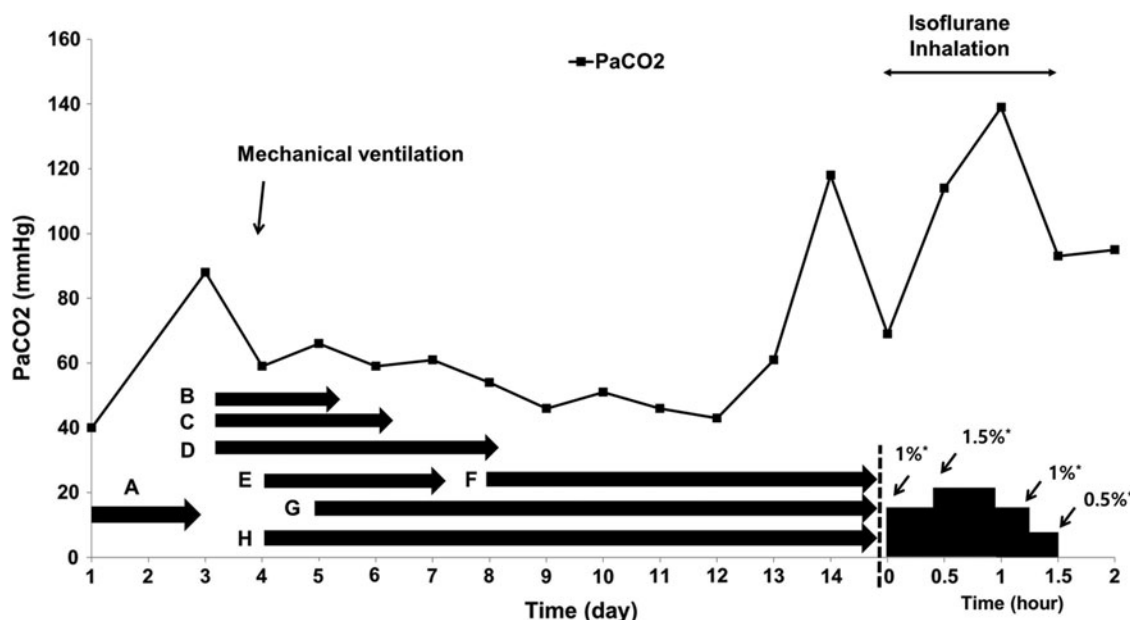


FIG. 4. Partial pressure of arterial carbon dioxide (PaCO_2) with management until and during isoflurane inhalation in Case 2, with A: oral corticosteroid (deflazacort); B: continuous IV infusion of aminophylline; C: nebulized albuterol; D: nebulized budesonide; E: methylprednisolone pulse therapy; F: IV dexamethasone; G: nebulized ipratropium bromide; and H: IV midazolam, ketamine, and fentanyl with muscle relaxant (atracurium). *Isoflurane concentration. IV, intravenous.

improvement is consistent with prior reports in asthmatic children.^{8,12}

CLD patients often report abnormal lung function, with varying degrees of airway obstruction, bronchial hyperresponsiveness (BHR), and impaired gas diffusing capacity.¹³ BHR is a documented feature of both bronchopulmonary dysplasia (BPD) and asthma, but the BHR of BPD is less well understood, and it is likely that multiple different mechanisms are responsible.¹⁴ Recent data suggest the presence of a neutrophilic airway inflammation in CLD, possibly reflecting mechanisms resembling those underlying chronic obstructive pulmonary disease.¹⁵ Still the practical approach to small airway obstruction in CLD is generally analogous to asthma.¹⁶

Recently, many studies have reported that volatile anesthetics also have immunosuppressive or anti-inflammatory effects.¹⁷ In particular, isoflurane exposure causes reduction in levels of systemic proinflammatory cytokines (TNF- α , IL-1 β , and IL-6) and leukocyte counts, as well as less macrophage activation and polarization toward the M2 phenotype. These effects were found to be protein kinase C dependent and also on account of systemic inhibition of NF- κ B.^{18,19} With these anti-inflammatory properties, inhaled isoflurane could be attributable to further bronchodilation in the first case after conventional therapies.

Conversely, the second case had BOS, which is the most common late pulmonary complication after uPBSCT. BOS is a fibroproliferative process characterized by submucosal inflammation and fibrosis of the bronchiolar walls, finally causing complete obliteration of the airway lumen. The functional consequence of this process is progressive and largely irreversible airflow obstruction.²⁰ Pathogenesis of BOS is uncertain, but donor T lymphocytes, inflammatory mediators, and cytokines were suspected to play a key role.²¹ The incidence of BOS in allogeneic hematopoietic stem cell transplantation recipients ranges from 0% to 48%.²² It is characterized by the

onset of new airflow obstructions following transplantation (e.g., FEV₁ <75% predicted in spirometry), accompanied by dry cough and dyspnea. BOS patients mostly have a slow progressive course with episodes of acute exacerbation of airway obstruction. During acute exacerbations of respiratory symptoms, although the use of bronchodilators is mandatory, patient improvement is not always certain^{22,23} and there is no consensus on the management.

We applied initially conventional asthma exacerbation management for bronchodilation, but it was not effective at all, and so, we applied isoflurane inhalation expecting known bronchodilation and immune modulation effect, but the poor response in BOS patient could be attributed by either the feature of irreversible airflow obstruction as part of acute progression of BOS or the inability of inhaled isoflurane to be delivered to the airways due to severe bronchospasm.

The advantages of inhalation anesthetics in ICU settings are known as follows: more reliable route of administration and elimination, no withdrawal symptoms, easy control of sedation level, and no development of tolerance.^{24–26} When using inhalation anesthetics in bronchospasm, anesthesia-capable ventilatory support and volatile anesthesia gas scavenging system are essential. The monitoring equipment should include end-tidal CO₂, cardiorespiratory support with pulse oximetry, arterial access for BP, and blood gas monitoring, also central venous access for volume status monitoring and administration of medications.^{8,12}

The major limitation in using anesthetics for bronchospasm in an ICU setting is the practical challenge in administering the inhaled anesthetics outside of the operating room. In 2005, the anesthetic conserving device, AnaConDa® (AnaConDa, Sedana Medical, Uppsala, Sweden), was marketed for ICU sedation with volatile anesthetics. The AnaConDa is incorporated into the respiratory circuit between the Y-piece and converts the VA from liquid to vapor.

It can be used with any standard ICU ventilator, consequently making it possible to deliver anesthetic agents easily and safely in an ICU setting.²⁷

Although there was no standard protocol for isoflurane inhalation, an initial dose, ~0.5%–2%, was usually increased by 0.1% every 5–10 min until either clinical or laboratory improvement of bronchospasm was evident.^{2,12} Once an appropriate response has been achieved, the concentration was maintained for several hours, before being decreased by 0.1% every 30–60 min.^{2,8,12} The duration of isoflurane therapy varies according to the patient's condition or protocols.

Although hypotension via direct vasodilation is an expected complication of isoflurane inhalation therapy, it is generally responsive to volume support or inotropic agents and thought to be short lived.^{8,28} In the cases reported here, although hypotension developed in both patients, BP soon recovered and was sustained within the normal range after administration of inotropics. Hepatic and renal injury, another expected complication, can be primarily attributed to the toxic metabolites of halogenated vapors, that is, fluoride ions.^{12,25,28} In the current cases, we did not monitor serum fluoride levels, yet there was no evidence of renal or hepatic dysfunction, consistent with previous reports.^{2,12}

In conclusion, isoflurane can be considered for children with severe bronchospasm refractory to conventional therapies. However, the response could differ due to an underlying disease; hence, further studies are warranted to evaluate the usefulness and cost-effectiveness of treating disease that causes bronchospasm with inhalation anesthetics.

Acknowledgment

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Disclosure Statement

No competing financial interests exist.

References

- Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H. Mechanism of action of inhalational anesthesia on airways. *Anesthesiology* 1982; 56:107–111.
- Shankar V, Churchwell KB, Deshpande JK. Isoflurane therapy for severe refractory status asthmaticus in children. *Intensive Care Med* 2006; 32:927–933.
- Rooke GA, Choi JH, Bishop MJ. The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. *Anesthesiology* 1997; 86:1294–1299.
- Vaschetto R, Bellotti E, Turucz E, Gregoretti C, Corte FD, Navalesi P. Inhalational anesthetics in acute severe asthma. *Curr Drug Targets* 2009; 10:826–832.
- Paulissian R, Mahdi M, Joseph NJ, Salem MR, Pavlovich B, Crystal GJ. Hemodynamic responses to pancuronium and vecuronium during high-dose fentanyl anesthesia for coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 1991; 5:120–125.
- Koninckx M, Buysse C, de Hoog M. Management of status asthmaticus in children. *Paediatr Respir Rev* 2013; 14:78–85.
- Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. *J Am Coll Cardiol* 2014; 63:2769–2778.
- Turner DA, Heitz D, Cooper MK, Smith PB, Arnold JH, Bateman ST. Isoflurane for life-threatening bronchospasm: a 15-year single-center experience. *Respir Care* 2012; 57:1857–1864.
- Megarbane A, Souraty N, Prieur M, Theophile D, Chédid P, Augé J, Vekemans M. Interstitial duplication of the short arm of chromosome 2: report of a new case and review. *J Med Genet* 1997; 34:783–786.
- Say B, Carpenter NJ, Giacoia G, Jegathesan S. Agenesis of the lung associated with a chromosome abnormality (46,XX,2p+). *J Med Genet* 1980; 17:477–478.
- Eber E, Zach MS. Long term sequelae of bronchopulmonary dysplasia (chronic lung disease of infancy). *Thorax* 2001; 56:317–323.
- Wheeler DS, Clapp CR, Ponaman ML, Bsn HM, Poss WB. Isoflurane therapy for status asthmaticus in children: a case series and protocol. *Pediatr Crit Care Med* 2000; 1:55–59.
- Clemm HH, Engeseth M, Vollsaeter M, Kotecha S, Halvorsen T. Bronchial hyper-responsiveness after preterm birth. *Paediatr Respir Rev* 2018; 26:34–40.
- Royce SG, Nold MF, Bui C, Donovan C, Lam M, Lamanna E, Rudloff I, Bourke JE, Nold-Petry CA. Airway remodeling and hyperreactivity in a model of bronchopulmonary dysplasia and their modulation by IL-1 receptor antagonist. *Am J Respir Cell Mol Biol* 2016; 55:858–868.
- Carraro S, Filippone M, Da Dalt L, Ferraro V, Maretti M, Bressan S, El Mazloum D, Baraldi E. Bronchopulmonary dysplasia: the earliest and perhaps the longest lasting obstructive lung disease in humans. *Early Hum Dev* 2013; 89 Suppl 3:S3–S5.
- Abman SH, Collaco JM, Shepherd EG, Keszler M, Cuevas-Guaman M, Welty SE, Truog WE, McGrath-Morrow SA, Moore PE, Rhein LM, Kirpalani H, Zhang H, Gratny LL, Lynch SK, Curtiss J, Stonestreet BS, McKinney RL, Dysart KC, Gien J, Baker CD, Donohue PK, Austin E, Fike C, Nelin LD; Bronchopulmonary Dysplasia Collaborative. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr* 2017; 181:12–28.e1.
- Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y. Immune modulation by volatile anesthetics. *Anesthesiology* 2016; 125:399–411.
- Cruz FF, Rocco PR, Pelosi P. Anti-inflammatory properties of anesthetic agents. *Crit Care* 2017; 21:67.
- Lee YM, Song BC, Yeum KJ. Impact of volatile anesthetics on oxidative stress and inflammation. *Biomed Res Int* 2015; 2015:242709.
- Kotloff RM, Keshavjee S. Lung transplantation. In: Broaddus VC, Mason RJ, Ernst JD, et al., eds. *Murray and Nadel's Textbook of Respiratory Medicine*, 6th ed. Philadelphia: Elsevier Saunders, 2016.
- Peters SG. Is bronchiolitis obliterans after hematopoietic stem cell transplantation reversible? *Am J Respir Crit Care Med* 2015; 191:1214–1216.
- Soubani AO, Uberti JP. Bronchiolitis obliterans following haematopoietic stem cell transplantation. *Eur Respir J* 2007; 29:1007–1019.
- Ditschkowski M, Elmaagacli AH, Koldehoff M, Gromke T, Trenchel R, Beelen DW. Bronchiolitis obliterans after allogeneic hematopoietic SCT: further insight—new perspectives? *Bone Marrow Transplant* 2013; 48:1224–1229.

24. Tanigami H, Yahagi N, Kumon K, Watanabe Y, Haruna M, Matsui J, Hayashi H. Long-term sedation with isoflurane in postoperative intensive care in cardiac surgery. *Artif Organs* 1997; 21:21–23.
25. Spencer EM, Willatts SM. Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety. *Intensive Care Med* 1992; 18:415–421.
26. Soukup J, Scharff K, Kubosch K, Pohl C, Bomplitz M, Komparadt J. State of the art: sedation concepts with volatile anesthetics in critically ill patients. *J Crit Care* 2009; 24:535–544.
27. Misra S, Koshy T. A review of the practice of sedation with inhalational anaesthetics in the intensive care unit with the AnaConDa((R)) device. *Indian J Anaesth* 2012; 56:518–523.
28. Johnston RG, Noseworthy TW, Friesen EG, Yule HA, Shustack A. Isoflurane therapy for status asthmaticus in children and adults. *Chest* 1990; 97:698–701.

Address correspondence to:

Yoon Hee Kim, MD

*Division of Pediatric Pulmonology
and Pediatric Critical Care Medicine*

Department of Pediatrics

Severance Hospital

Yonsei University College of Medicine

50-1 Yonsei-ro

Seodaemun-gu

Seoul 03722

Korea

E-mail: yhkim@yuhs.ac

Received for publication September 25, 2017; accepted after revision March 17, 2018.