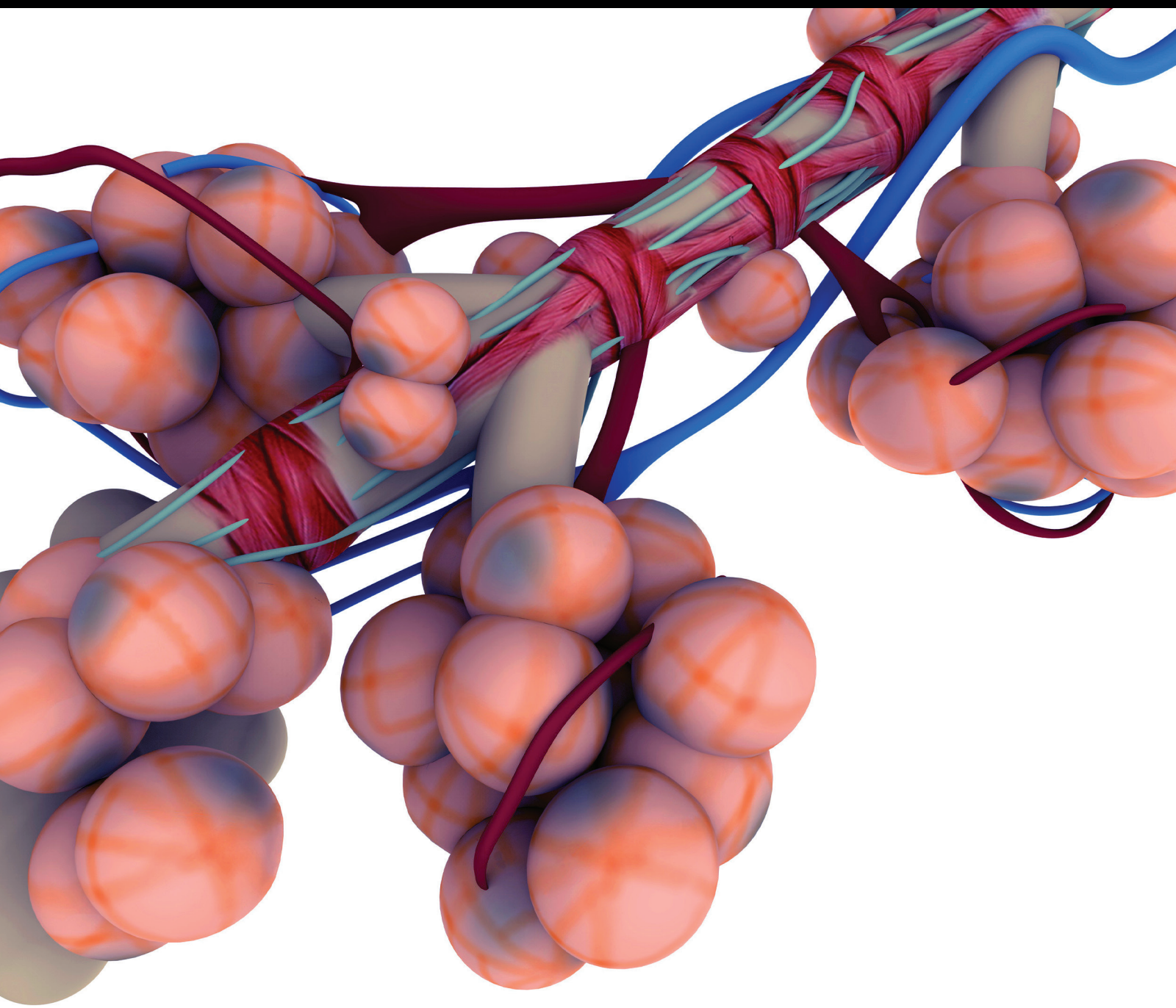
Canadian Respiratory Journal

Oxygen Therapy and Ventilatory Support

Guest Editors: Wan-Jie Gu, Jan Bakker, Zhongheng Zhang, and Sven Van Poucke



Oxygen Therapy and Ventilatory Support

Canadian Respiratory Journal

Oxygen Therapy and Ventilatory Support

Guest Editors: Wan-Jie Gu, Zhongheng Zhang,
and Sven Van Poucke

Editorial Board

Contents

Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 2462818, 2 pages
https://doi.org/10.1155/2017/2462818

Editorial

Oxygen Therapy and Ventilatory Support

Wan-Jie Gu,[1] Zhongheng Zhang,[2] and Sven Van Poucke[3]

[1]*Department of Anesthesiology, Nanjing Drum Tower Hospital, Medical College of Nanjing University, Nanjing, China*
[2]*Department of Emergency Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, China*
[3]*Ziekenhuis Oost-Limburg, Genk, Belgium*

Correspondence should be addressed to Zhongheng Zhang; zh_zhang1984@hotmail.com

Received 12 April 2017; Accepted 12 April 2017; Published 14 May 2017

When Joseph Priestley discovered oxygen in 1774, he found that air was a mixture of gases. He called one of these gases "dephlogisticated air," to which later the chemist Antoine Lavoisier gave the name "oxygen" which made candles burn brighter and longer than ordinary air [1]. Until now, this discovery covers 2 essential features of oxygen which in clinical practice results in the use of oxygen as a drug. In clinical practice, oxygen can be life-saving by giving to patients with tissue hypoxemia. However, too much oxygenation can cause toxicity, which has been well described in the literature. Oxygen toxicity in central nervous system is termed Paul Bert effect and in the lung it is termed Lorrain Smith effect. The Paul Bert effect results in seizures from which the onset depends upon the partial pressure of oxygen in the breathing gas and exposure duration. This effect is well known among divers and in hyperbaric facilities. Respiratory side effects from oxygen are more frequently observed in critical care settings resulting in a restrictive policy not to administer more oxygen than required. In this context, however, it is important to have the formulae of oxygen content in mind while not just relying on the oxygen saturation values (arterial oxygen content = $(\mathrm{Hb} \times 1.34 \times \mathrm{SaO_2}) + (0.0031 \times \mathrm{PaO_2})$). Additionally, NICU patients are potentially at risk for Terry's syndrome or retinopathy of prematurity, a disease of the eye when oxygen is administered for premature development of the lungs. Although oxygen is a natural molecule, the complexity of its interactions with human metabolism continues to be a subject for in-depth research [2].

In this thematic issue of oxygen therapy and ventilatory support (OTVS), several papers investigated and discussed some key aspects in the field of respiratory failure and ventilator support. J.-L. Vincent et al. published an article addressing the harmful effect of hyperoxia on critical illness. It has been reported that the effect of partial pressure of arterial oxygenation on mortality follows a quadratic function [3], and there is nadir at which the mortality rate is the lowest. Respiratory support can be performed by a variety of techniques, ranging from the simple oxygen therapy to complex extracorporeal membrane oxygenation (ECMO). In patients with ECMO, the mechanical ventilation usually plays an important role. The appropriate setting of the ventilator is of vital importance to provide oxygen supply to vital organs while avoiding lung injury. It is an art and science where, in most circumstances, there is a lack of high-level evidence from randomized controlled trials. Z. Zhang and colleagues discussed some important aspects on the use of mechanical ventilation in patients with ECMO. S. Ye and his colleagues investigated the effect of antipyretic therapy on mortality outcome in patients receiving mechanical ventilation. The study employed the MIMIC-II database as the source of data [4]. The database is freely available to the public and is the gold standard of the critical care big data. It provides in-hospital clinical data with high granularity, and data mining using such database can provide insights into complex interactions between disease severity, medical treatment, and procedures. Such complex interactions may not be feasible in conventional randomized controlled trials (RCTs). Also, traditional RCTs are designed to explore the biological efficacy of a certain intervention, which may not be applicable to real world settings where the clinical effectiveness is most highlighted. There is evidence that the results obtained from RCTs can be different from that obtained by observational studies [5].

Wan-Jie Gu
Zhongheng Zhang
Sven Van Poucke

References

[1] J. B. West, "Joseph Priestley, oxygen, and the Enlightenment," *American Journal of Physiology—Lung Cellular and Molecular Physiology*, vol. 306, no. 2, pp. L111–L1119, 2014.

[2] S. Van Poucke, P. Jorens, and L. Beaucourt, "Physiologic effects of hyperbaric oxygen on ischemia-reperfusion phenomenon rachmaninov's third piano concerto in hyperbaric physiology," in *Handbook on Hyperbaric Medicine*, pp. 121–134, Dordrecht Publisher: Springer Netherlands, 2006.

[3] Z. Zhang and X. Ji, "Quadratic function between arterial partial oxygen pressure and mortality risk in sepsis patients: an interaction with simplified acute physiology score," *Scientific Reports*, vol. 6, Article ID 35133, 2016.

[4] Z. Zhang, "Accessing critical care big data: a step by step approach," *Journal of Thoracic Disease*, vol. 7, no. 3, pp. 238–242, 2015.

[5] Z. Zhang, H. Ni, and X. Xu, "Observational studies using propensity score analysis underestimated the effect sizes in critical care medicine," *Journal of Clinical Epidemiology*, vol. 67, no. 8, pp. 932–939, 2014.

Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 8074678, 5 pages
https://doi.org/10.1155/2017/8074678

Research Article

Clara Cell Protein Expression in Mechanically Ventilated Term and Preterm Infants with Respiratory Distress Syndrome and at Risk of Bronchopulmonary Dysplasia: A Pilot Study

José Guzmán-Bárcenas,[1,2] Antonio Calderón-Moore,[2] Héctor Baptista-González,[1] and Claudine Irles[3]

[1]*Department of Perinatal Hematology, Instituto Nacional de Perinatología Isidro Espinoza de los Reyes, Montes Urales 800, 11000 Lomas de Virreyes, CDMX, Mexico*
[2]*Neonatal Intensive Care Unit, Hospital Infantil de México, Dr. Márquez No. 162, Cuauhtémoc, 06720 Doctores, CDMX, Mexico*
[3]*Department of Physiology and Cellular Development, Instituto Nacional de Perinatología Isidro Espinoza de los Reyes, Montes Urales 800, 11000 Lomas de Virreyes, CDMX, Mexico*

Correspondence should be addressed to Claudine Irles; claudine.irles@inper.gob.mx

Received 28 October 2016; Revised 25 February 2017; Accepted 16 March 2017; Published 11 April 2017

Academic Editor: Zhongheng Zhang

The aim of this pilot study was to determine Clara cell protein (CC16) concentration in bronchoalveolar lavages (BAL) fluid from full-term and preterm (<37 weeks' gestational age) neonates requiring respiratory support, having symptoms of neonatal respiratory distress syndrome, and at risk of bronchopulmonary dysplasia (BPD). We hypothesized that CC16 may be predictive of BPD diagnosis regardless of gestational age. BAL fluid CC16 was measured by ELISA at birth and at day 7 of life. Both groups that developed BPD showed significantly decreased BAL fluid CC16 levels compared to those infants that did not develop the disease. CC16 positively correlated with diagnosis of BPD and negatively with the severity of the disease. These results suggest that BAL fluid CC16 levels may have a diagnostic value at day 7 for BPD in both term and preterm infants. This study demonstrates the potential utility of BAL fluid CC16 levels as a biomarker for BPD in term infants.

1. Introduction

Bronchopulmonary dysplasia (BPD) also called chronic lung disease (CLD) of infancy is a neonatal-pediatric disease associated with lung injury in preterm infants or anomalous lung development in full-term neonates [1–3] and is usually associated with neonatal respiratory distress syndrome (RDS). BPD has been linked with long term pulmonary morbidity and function [4] and neurodevelopmental sequelae [5] during infancy. BPD is physiologically defined by NIH Workshops [6–8] as a requirement for supplemental oxygen for >28 days and severity of the disease is graded according to gestational age (necessity for mechanical ventilation occurs in severe BPD). However, it requires a period of time before BPD diagnosis and severity is determined. Therefore, biomarkers that allow early diagnosing and grading severity of BPD should be very useful to early predict this disease.

Clara cell secretory protein of 10–16 kDa (CC16), also known as CC10, Club cell protein, CCSP, or uteroglobin [9, 10], a member of the secretoglobin family [11], is the most abundant protein in bronchoalveolar lavage (BAL) fluid or tracheal aspirates (TA) from neonates [12, 13]. CC16 plays anti-inflammatory, immunomodulatory, and airway repairing roles [14–16]. Available studies have identified CC16 as a potential marker for BPD in preterm infants (reviewed by [17, 18]) but with contradictory results with either decreased [19, 20] or increased [21] cord blood CC16 levels or lower TA CC16 levels [13]. However, CC16 studies in full-term infants at risk of developing BPD are still scarce. Here we tested the hypothesis that CC16 may be predictive of BPD

diagnosis regardless of gestational age. Therefore, the aim of this exploratory pilot study was to determine CC16 levels in BAL fluid from term and preterm infants with respiratory failure, mechanically ventilated that subsequently developed BPD.

2. Materials and Methods

The Institutional responsible Ethical Committee and Research Committee of the National Institute of Perinatology *Isidro Espinoza de los Reyes* approved the study (#212250-19071) and signed informed consent was obtained. The study was conducted according to the Declaration of Helsinki (1964) ethic principles for human participants.

2.1. Clinical Characteristics. Ten newborns were included in the study: term (>37 weeks' gestation) and preterm (28–36 weeks' gestation) neonates who required endotracheal intubation for mechanical ventilation for more than 7 days and diagnosis of failure of ventilation treatment (3), with signs and symptoms of neonatal respiratory distress syndrome (RDS), in whom bronchopulmonary dysplasia (BPD) was diagnosed subsequently ($n = 5$) or not ($n = 5$). Clinical data was collected from medical records such as gestational age, birth weight, gender, Apgar score, prenatal steroids, and surfactant treatment. One infant had prophylactic surfactant, one neonate received rescue surfactant, and, finally, one infant had one more dose of rescue surfactant. Exclusion criteria were infants with chromosomal abnormalities, congenital lung and heart diseases, and malformations. The clinical characteristics of the study population are depicted in Table 1.

2.2. Clinical Characteristics of Term Neonates. Only term neonates presented the following characteristics: septic shock (two neonates) and transitory tachypnea of the newborn (three neonates) with two of the latter newborns also developing transitory pulmonary hypertension. Therefore, neonatal mechanical ventilation was secondary to the initial diagnosis.

BPD diagnosis and severity were defined according to the National Institute of Child Health and Human Development (NICHD) and National Heart, Lung, and Blood Institute (NHLBI) Workshops [6–8]: Grade 1 BPD (mild): supplemental oxygen for at least 28 days and on room air at 36 weeks' PMA/discharge (for infants < 32 weeks at birth) or at 56 days/discharge (for infants > 32 weeks at birth); Grade 2 BPD (moderate): supplemental oxygen for at least 28 days and receiving supplemental effective oxygen < 30% at 36 weeks/discharge (for infants < 32 weeks at birth) or 56 days/discharge (for infants > 32 weeks at birth); Grade 3 BPD (severe): supplemental oxygen for at least 28 days and receiving supplemental effective oxygen > 30% or on nasal CPAP or mechanical ventilation at 36 weeks/discharge (for infants < 32 weeks at birth) or 56 days/discharge (for infants > 32 weeks at birth) [8].

2.3. Collection of Samples and CC16 Determination. Bronchoalveolar lavages (BAL) fluid samples were collected only when indicated clinically (i.e., endotracheal intubation), at day 1 (birth) and day 7 (1 week). A nonbronchoscopic method was used to obtain tracheal aspirate. Briefly, after tracheal intubation, a fixed volume of saline solution (0.5 mL) was applied and immediately aspirated (the recovered volume was 0.3 mL). The fluid was kept at all times at 4°C, under ice, and transported to the laboratory within 30 min after its collection. Samples were immediately centrifuged for 10 min at 3500 rpm/4°C and the supernatant was frozen at −70°C. Total protein concentration in BAL samples was determined by Bradford assay (Bio-Rad, California, USA). CC16 protein concentration was assayed in BAL fluid in duplicate by a commercial CC16 ELISA kit (RD191022200, Biovendor, Brno, Czech Republic) with an intra-assay coefficients of variation (CV) of 3.4% and interassay CV of 4.7%.

Table 1: Clinical characteristics in neonates without or with BPD*.

	No BPD ($n = 5$)	BPD ($n = 5$)
Gender Female, male	3, 2	2, 3
Gestational age (weeks)	34.2 ± 2.2 [28–39]	34.8 ± 1.8 [29–39]
Preterm < 36 weeks	3	2
Term > 37 weeks	2	3
Birthweight (g)	2120 ± 453 [750–3150]	2266 ± 462 [900–3250]
Apgar score at 1 min	6.2 [5–7]	7
Apgar score at 5 min	7.4 [5–8]	7.8 [7-8]
GDM	0	1
Chorioamnionitis	0	1
Preeclampsia	0	2
IUGR	2	3
Death	0	1
Prenatal steroids	0	1
Prophylactic surfactant	0	1
Atelectasis	3	1

*Values are depicted as mean ± SEM, [range], or number of individuals.
GDM: gestational diabetes mellitus; IUGR: intrauterine growth restriction.

2.4. Statistical Analysis. Results are expressed as mean ± SEM, [range], or number of individuals as appropriate. Statistical differences were assessed by Mann–Whitney U, two-tailed test [22]. Correlations were evaluated using Pearson test. For all analysis, values of $^{*}p < 0.05$ and $^{**}p < 0.01$ were considered to be statistically significant. Analysis was performed by SPSS 16.0 software (IBM, Armonk, NY, USA).

3. Results

In this pilot study, the objective was to determine Clara cell protein (CC16) concentration in BAL fluid from term

Table 2: BAL fluid CC16 concentration in ventilated term and preterm neonates from day 1 and day 7.

	GE (weeks)	BAL CC10 (ng/ml)				BPD severity
		No BPD		BPD		
		Day 1	*Day 7*	*Day 1*	*Day 7*	
Neonate 1	37	—	—	0.89	0.35	II
Neonate 2	37	—	—	0.36	0.26	II
Neonate 3	38	2.84	0.49	—	—	no
Neonate 4	39	2.13	1.32	—	—	no
Neonate 5	39	—	—	0.097	0.12	III
Neonate 6	28	1.63	1.73	—	—	no
Neonate 7	29	—	—	0.35	0.23	II
Neonate 8	30	4.89	1.53	—	—	no
Neonate 9	32	—	—	0.45	0.47	I
Neonate 10	36	2.33	0.27	—	—	no
Mean		2.76	1.07	0.43	0.29	
SEM		0.57	0.29	0.13	0.06	

and preterm infants with respiratory failure in whom bronchopulmonary dysplasia (BPD) was diagnosed subsequently. All neonates required ventilatory support for more than 7 days. The peak inspiratory pressure exceeded 17 cm H_2O in six infants. BPD was diagnosed in five infants from which three were term and two were preterm neonates. One neonate presented Grade 1 BPD (one preterm neonate), three neonates Grade 2 BPD (two term and one preterm neonates), and one neonate Grade 3 BPD (one term neonate). The clinical characteristics are depicted in Table 1. Five neonates presented an appropriate for gestational age weight while the other five had a weight of less than 2500 g. Intrauterine growth restriction (IUGR) was diagnosed in five infants. Maternal conditions were gestational diabetes mellitus in one neonate, chorioamnionitis in one infant, and preeclampsia in two neonates. Prophylactic surfactant was administered in one of the infants.

BAL fluid CC-10 levels were found significantly diminished in neonates that developed BPD compared to those that did not develop the disease (0.43 ng/mL ± 0.13 versus 2.76 ng/mL ± 0.57, $p = 0.0079^{**}$ in day 1 and 0.29 ng/mL ± 0.06 versus 1.07 ng/mL ± 0.29, $p = 0.0317^{*}$ in day 7; Table 2) with no statistical differences between term and preterm infants. BAL fluid CC-10 concentrations obtained at day 7 were found to be decreased in comparison with day 1 ($p = 0.0159^{*}$ and $p = 0.5476$ without or with BPD, resp.; Table 2).

There was a significant correlation between both CC16 determinations in BAL with BPD diagnosis ($r = 818^{**}$, $p = 0.004$ and $r = 683^{*}$, $p = 0.029$, two tails for days 1 and 7, resp.) and severity of the disease ($r = -0.769^{**}$, $p = 0.009$ and $r = -0.680^{*}$, $p = 0.031$, two tails for days 1 and 7, resp.). Furthermore, CC16 levels at day 1 also correlated with maximal weight loss at day 7 (15% of total weight) ($r = -0.695$, $^{*}p = 0.026$, two tails). IUGR, prophylactic, and rescue surfactant did not correlate significantly with any variable.

These results suggest that BAL fluid CC16 levels have a diagnostic value on day 7 for BPD in both term and preterm infants.

4. Discussion

Both term and preterm neonates that developed BPD had lower BAL fluid CC16 levels in comparison with neonates that did not develop the disease. This pilot study is in agreement with previous studies for preterm infants [14, 23] but provides further evidence for term infants. Furthermore, CC16 levels at birth were found to positively correlate with BPD diagnosis and negatively with severity. These results suggest that BAL fluid CC16 concentration will be able to help to early discriminate between infants with none, mild, moderate, and severe BPD, independently of gestational age.

Interestingly, CC16 levels also correlated with optimal weight gain and this result may point to the importance of optimal nutrition for repairing lung injury and increasing the energy needs caused by BPD.

The physiopathological mechanisms of BPD in term and preterm infants are probably different. Preterm birth is associated with lung immaturity, oxygen toxicity (oxygen free radical exposure), and mechanical ventilation (reviewed by [24, 25]). Further research is needed in order to elucidate the mechanisms of BPD in term neonates which is probably distinct in preterm neonates.

It has been shown in a mouse model that CC16 administration increases epithelial proliferation, protects against oxidative stress [26], and is suggested to be linked to a population of Clara cells, producing CC16 protein, with a bone marrow (BMC) phenotype which would be implicated in lung repair by reducing pulmonary inflammation and promoting airway regeneration [27]. In our neonates, it is possible that the low levels of CC16 protein related to BPD severity are due to a diminished number of Clara cells affecting lung recovery.

4.1. Limitations of the Study. We acknowledge that the results and analysis are limited by the very small sample size; however, we developed this pilot study with the intention to incorporate a wider study in our own center and other centers based on the obtained results. This exploratory work will contribute to the development of a subsequent study by the information obtained of BAL CC16 concentration in BPD.

5. Conclusions

BAL fluid CC16 levels were found to be decreased in both term and preterm ventilated neonates who subsequently developed BPD. CC16 levels at day 7 may be useful to diagnose the disease. This study demonstrates the potential utility of BAL fluid CC16 levels as a biomarker for BPD in term infants.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

This work was supported by the Instituto Nacional de Perinatología *Isidro Espinoza de los Reyes* [Grant no. 212250-19071 to Guzmán-Bárcenas José].

References

[1] K. M. Deakins, "Bronchopulmonary dysplasia," *Respiratory Care*, vol. 54, no. 9, pp. 1252–1262, 2009.

[2] A. Bhandari and V. Bhandari, "Bronchopulmonary dysplasia: an update," *Indian Journal of Pediatrics*, vol. 74, no. 1, pp. 73–77, 2007.

[3] A. Greenough, M. Premkumar, and D. Patel, "Ventilatory strategies for the extremely premature infant," *Paediatric Anaesthesia*, vol. 18, no. 5, pp. 371–377, 2008.

[4] E. Eber and M. S. Zach, "Long term sequelae of bronchopulmonary dysplasia (chronic lung disease of infancy)," *Thorax*, vol. 56, no. 4, pp. 317–323, 2001.

[5] E. J. Short, N. K. Klein, B. A. Lewis et al., "Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes," *Pediatrics*, vol. 112, no. 5, article e359, 2003.

[6] A. H. Jobe and E. Bancalari, "Bronchopulmonary dysplasia," *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 7, pp. 1723–1729, 2001.

[7] R. A. Ehrenkranz, M. C. Walsh, B. R. Vohr et al., "Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia," *Pediatrics*, vol. 116, no. 6, pp. 1353–1360, 2005.

[8] R. M. Ryan, "A new look at bronchopulmonary dysplasia classification," *Journal of Perinatology*, vol. 26, no. 4, pp. 207–209, 2006.

[9] F. Broeckaert and A. Bernard, "Clara cell secretory protein (CC16): characteristics and perspectives as lung peripheral biomarker," *Clinical and Experimental Allergy*, vol. 30, no. 4, pp. 469–475, 2000.

[10] G. Singh and S. L. Katyal, "Clara cells and clara cell 10 kD protein (CC10)," *American Journal of Respiratory Cell and Molecular Biology*, vol. 17, no. 2, pp. 141–143, 1997.

[11] J. Klug, H. M. Beier, A. Bernard et al., "Uteroglobin/clara cell 10-kDa family of proteins: nomenclature committee report," *Annals of the New York Academy of Sciences*, vol. 923, pp. 348–354, 2000.

[12] J. Arias-Martínez, M. Palacios-Sánchez, D. Delgado-Franco et al., "Clara cell protein expression in human neonates during respiratory distress syndrome," *Cellular Physiology and Biochemistry*, vol. 29, no. 5-6, pp. 753–760, 2012.

[13] P. L. Ramsay, F. J. DeMayo, S. E. Hegemier, M. E. Wearden, C. V. Smith, and S. E. Welty, "Clara cell secretory protein oxidation and expression in premature infants who develop bronchopulmonary dysplasia," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 1, pp. 155–161, 2001.

[14] F. Broeckaert, A. Clippe, B. Knoops, C. Hermans, and A. Bernard, "Clara cell secretory protein (CC16): features as a peripheral lung biomarker," *Annals of the New York Academy of Sciences*, vol. 923, pp. 68–77, 2000.

[15] C.-H. Hung, L.-C. Chen, Z. Zhang et al., "Regulation of TH2 responses by the pulmonary Clara cell secretory 10-kd protein," *Journal of Allergy and Clinical Immunology*, vol. 114, no. 3, pp. 664–670, 2004.

[16] J. A. Kropski, R. D. Fremont, C. S. Calfee, and L. B. Ware, "Clara cell protein (CC16), a marker of lung epithelial injury, is decreased in plasma and pulmonary edema fluid from patients with acute lung injury," *Chest*, vol. 135, no. 6, pp. 1440–1447, 2009.

[17] L. Rivera, R. Siddaiah, C. Oji-Mmuo, G. R. Silveyra, and P. Silveyra, "Biomarkers for bronchopulmonary dysplasia in the preterm infant," *Frontiers in Pediatrics*, vol. 4, article 33, 2016.

[18] A. Trembath and M. M. Laughon, "Predictors of bronchopulmonary dysplasia," *Clinics in Perinatology*, vol. 39, no. 3, pp. 585–601, 2012.

[19] A. J. J. Schrama, A. Bernard, B. J. H. M. Poorthuis, A. H. Zwinderman, H. M. Berger, and F. J. Walther, "Cord blood Clara cell protein CC16 predicts the development of bronchopulmonary dysplasia," *European Journal of Pediatrics*, vol. 167, no. 11, pp. 1305–1312, 2008.

[20] K. Wang, X. Huang, H. Lu, and Z. Zhang, "A comparison of kl-6 and clara cell protein as markers for predicting bronchopulmonary dysplasia in preterm infants," *Disease Markers*, vol. 2014, Article ID 736536, 2014.

[21] K. Sarafidis, T. Stathopoulou, E. Diamanti et al., "Clara cell secretory protein (CC16) as a peripheral blood biomarker of lung injury in ventilated preterm neonates," *European Journal of Pediatrics*, vol. 167, no. 11, pp. 1297–1303, 2008.

[22] Z. Zhang, "Univariate description and bivariate statistical inference: the first step delving into data," *Annals of Translational Medicine*, vol. 4, no. 5, pp. 91–98, 2016.

[23] A. S. Loughran-Fowlds, J. W. Lin, J. Oei, J. Michalowski, R. Henry, and K. Lui, "Early postnatal surge of serum Clara cell secretory protein in newborn infants," *Neonatology*, vol. 101, no. 2, pp. 125–131, 2012.

[24] S. Niedermaier and A. Hilgendorff, "Bronchopulmonary dysplasia—an overview about pathophysiologic concepts," *Molecular and Cellular Pediatrics*, vol. 2, no. 1, p. 2, 2015.

[25] J. J. Coalson, "Pathology of bronchopulmonary dysplasia," *Seminars in Perinatology*, vol. 30, no. 4, pp. 179–184, 2006.

[26] M. L. Bustos, M. Mura, P. Marcus et al., "Bone marrow cells expressing clara cell secretory protein increase epithelial repair after ablation of pulmonary clara cells," *Molecular Therapy*, vol. 21, no. 6, pp. 1251–1258, 2013.

[27] M. L. Bustos, M. Mura, D. Hwang et al., "Depletion of bone marrow CCSP-expressing cells delays airway regeneration," *Molecular Therapy*, vol. 23, no. 3, pp. 561–569, 2015.

Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 3087505, 7 pages
https://doi.org/10.1155/2017/3087505

Research Article

Effect of Antipyretic Therapy on Mortality in Critically Ill Patients with Sepsis Receiving Mechanical Ventilation Treatment

Sheng Ye,[1] Dan Xu,[1] Chenmei Zhang,[1] Mengyao Li,[1] and Yanyi Zhang[2]

[1]*Pediatric Intensive Care Unit, The Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[2]*Psychological Department, The Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*

Correspondence should be addressed to Yanyi Zhang; doczyy1981@sina.com

Received 27 October 2016; Revised 15 January 2017; Accepted 14 February 2017; Published 12 March 2017

Academic Editor: Wan-Jie Gu

Purpose. The study aimed to investigate the effectiveness of antipyretic therapy on mortality in critically ill patients with sepsis requiring mechanical ventilation. *Methods*. In this study, we employed the multiparameter intelligent monitoring in intensive care II (MIMIC-II) database (version 2.6). All patients meeting the criteria for sepsis and also receiving mechanical ventilation treatment were included for analysis, all of whom suffer from fever or hyperthermia. Logistic regression model and R language (R version 3.2.3 2015-12-10) were used to explore the association of antipyretic therapy and mortality risk in critically ill patients with sepsis receiving mechanical ventilation treatment. *Results*. A total of 8,711 patients with mechanical ventilator were included in our analysis, and 1523 patients died. We did not find any significant difference in the proportion of patients receiving antipyretic medication between survivors and nonsurvivors (7.9% versus 7.4%, $p = 0.49$). External cooling was associated with increased risk of death (13.5% versus 9.5%, $p < 0.001$). In our regression model, antipyretic therapy was positively associated with mortality risk (odds ratio [OR]: 1.41, 95% CI: 1.20–1.66, $p < 0.001$). *Conclusions*. The use of antipyretic therapy is associated with increased risk of mortality in septic ICU patients requiring mechanical ventilation. External cooling may even be deleterious.

1. Introduction

Sepsis is a major threat to human health and is among the most important causes of morbidity and mortality in the intensive care unit (ICU). In 2010, sepsis accounted for approximately 5% of deaths in England [1]. Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. In the present time, organ dysfunction is defined in terms of a change in baseline Sequential Organ Failure Assessment (SOFA) score [2].

Fever, the cardinal symptom of sepsis, is common among patients admitted to the ICU. Some clinicians believe that fever is deleterious because it exacerbates the imbalance between oxygen supply and demand, and most will prescribe antipyretic therapy for fever control in order to relieve the symptom. In contrast, some clinicians consider fever as a protective response that can inhibit the growth of microorganisms, and suppression of fever may delay the recovery. These investigators do not recommend routine use of fever control in ICU patients with sepsis.

The management of fever induced by sepsis varies substantially across different institutions and hospitals [3, 4]. Circiumaru et al. conducted the first study on the relationship between fever and mortality in critically ill patients during their ICU stays and found that fever lasting more than 5 days was associated with increased mortality ($p < 0.001$) [5]. Barie et al. [6] were the first to study mortality risk in critically ill patients and recognized peak temperature as an important predictor of increased ICU mortality ($p < 0.001$). The most frequent ICU-acquired infection is ventilator-associated pneumonia [5–8], which can significantly increase patient length of stay, treatment costs, and mortality [9–12]. However, investigations into the effect of antipyretic therapy on mortality in patients with sepsis, especially those receiving mechanical ventilation treatment, are limited. One meta-analysis focused on the effect of antipyretic therapy on mortality in febrile ICU patients and reported no difference

between patients treated with and those without antipyretic therapy [13]. The results of observational studies and randomized controlled trials (RCT) are conflicting due to variations in study population, design, and methods of antipyretic therapy [14]. We assume that the effect of antipyretic therapy on mortality would be influenced by age, SOFA score, or other variables. A large clinical database was utilized in our study.

2. Methods

2.1. Patients. All patients meeting the criteria for sepsis and also receiving mechanical ventilation treatment were included for our study, all of whom suffer from fever or hyperthermia. Sepsis was defined according to the new consensus of the European Society of Intensive Care Medicine and the Society of Critical Care Medicine published in February 2016, with diagnosis based on the combination of infection and SOFA score ≥ 2 points [2]. The infection was defined if one of the following criteria was fulfilled: (1) ICD9 contains the term "infection" and "pneumonia," "lung," "abdomen," "bloodstream," or "renal or genitourinary tract" and (2) positive microbiological culture. All patients included in the present study had at least one recorded temperature greater than 37.2°C. Data management was performed by using the R language (R version 3.2.3 2015-12-10).

2.2. Study Protocol. The MIMIC-II (multiparameter intelligent monitoring in intensive care II) database (version 2.6) was employed for our study, which comprises deidentified health-related data associated with more than 40,000 patients who stayed in critical care units of the Beth Israel Deaconess Medical Center (Boston, MA) from 2001 to 2008. The MIMIC-II database includes demographics, vital signs, laboratory tests, medications, and other information. The author Z. Y. Y. obtained access to the database after completion of the NIH web-based training course "Protecting Human Research Participants." Data extraction was performed by using structure query language (SQL) with Navicat Premium Version 10.0.7. When the data were extracted, we considered antipyretic therapy to consist of antipyretic medication and external cooling. The former included drugs such as ibuprofen, acetaminophen, naproxen, ketoprofen, voltaren, diclofenac, and nimesulide. The latter included cooling blankets and ice packs. The SQL to extract body temperature measurements was as follows.

SELECT value1num, charttime, icustay_id FROM chartevents WHERE itemid = 677. From this query we obtained 783,632 body temperature measurements, representing all the measurements of body temperature recorded in the database at various sites of the body. ICU mortality, a solid outcome, was the main outcome criterion. Other variables including SOFA, age, Simplified Acute Physiology Score- (SAPS-) 1 [15], lactate levels, care unit type, and sex were also extracted.

2.3. Outcome Measures. The primary outcome measure was ICU mortality. Other variables such as SAPS-1 and SOFA scores, antipyretic therapy data, lactate levels, and care unit type were also included. The SAPS-1 is a disease severity classification system, which is valuable in that it can be averaged for a group of patients, and the calculation results in a predicted mortality. Its name stands for "Simplified Acute Physiology Score." The SOFA score is used to track a patient's status during ICU admission. It is a system to determine the extent of a person's organ function [16, 17].

2.4. Statistical Analysis. Variables were expressed as mean and standard deviation (SD), counts and percentages, or median and interquartile range [18]. As an effective prognostic indicator and evaluator for patient progress in ICU, the SOFA score was included in the model as one of the most important variables. The initial SOFA score is strongly correlated with mortality. Therefore, in the present study we extracted the sofa_first data.

Logistic regression model was used to examine the effect of antipyretic therapy on mortality in critically ill patients with sepsis receiving mechanical ventilation treatment [19]. The odds ratio of antipyretic therapy was calculated, with an OR > 1 indicating a positive coefficient of the antipyretic therapy group compared to the nonantipyretic therapy group. All statistical analyses were performed by using R language (R version 3.2.3 2015-12-10). A p value < 0.05 was considered significant.

3. Results

A total of 40,000 ICU patients were included in the MIMIC-II database (version 2.6), including 8,711 patients meeting the criteria of sepsis and also requiring mechanical ventilation.

In Table 1, many variables significantly differed between survivors and nonsurvivors. Survivors were younger than nonsurvivors. As expected, nonsurvivors had significantly higher SOFA and SAPS-1 scores. Admission to a MICU was associated with increased risk of death (50.3% versus 39%, $p < 0.001$), whereas patients in a CSRU were less likely to die (21.6% versus 35.4%, $p < 0.001$). External cooling was associated with increased risk of death (13.5% versus 9.5%, $p < 0.001$). However, there was no significant difference in the proportion of patients receiving antipyretic medication between survivors and nonsurvivors (7.9% versus 7.4%, $p = 0.49$).

As shown in Table 2, we conducted logistic regression analysis to adjust for confounding factors of antipyretic therapy by importing prespecified variables (age, SAPS-1, SOFA score, sex, care unit, and antipyretic therapy). In this regression model, antipyretic therapy was positively associated with mortality risk (odds ratio [OR]: 1.41, 95% CI: 1.20–1.66, $p < 0.001$) (OR = odds ratios).

Figure 1 shows the relationship between SOFA score and probability of death across different ICU sectors, with or without antipyretic therapy (antipyretic_both means external cooling and drug cooling). Probability of death for the fitted model was plotted on the y-axis and SOFA score on the x-axis. Here the red dotted line, which was fitted by parametric method, represents the predicted fitted value, and the result is shown with a black curved line fitted by nonparametric method. As shown in the figure, there was no obvious change, but there was a statistically significant difference between SOFA score and probability of death. Therefore, we

Table 1: Comparisons between survivors and nonsurvivors.

Variables	Overall (n = 8711)	Survivors (n = 7188)	Nonsurvivors (n = 1523)	p
Age (years)	66.1 (52.0, 77.5)	64.6 (50.9, 76.6)	71.3 (58.1, 81.2)	<0.001
SAPS-1	17 (14, 20)	16 (13, 20)	19 (16, 23)	<0.001
SOFA	8 (6, 11)	8 (6, 10)	10 (7, 14)	<0.001
Lactate level	0.84 ± 0.76	0.85 ± 0.79	0.75 ± 0.62	0.0002
Sex (male, %)	4866 (55.9)	4032 (56.1)	834 (54.8)	0.36
Care unit type* (%)				<0.001
MICU	3567 (40.9)	2801 (39.0)	766 (50.3)	
SICU	621 (7.1)	546 (7.6)	75 (4.9)	
CCU	1646 (18.9)	1293 (18.0)	353 (23.2)	
CSRU	2877 (33.0)	2548 (35.4)	329 (21.6)	
External cooling (n, %)	892 (10.2)	686 (9.5)	206 (13.5)	<0.001
Drug cooling (n, %)	652 (7.5)	531 (7.4)	121 (7.9)	0.49
Any antipyretic (n, %)	1385 (15.9)	1102 (15.3)	283 (18.6)	0.002

MICU, medical intensive care unit; SICU, surgical intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

Table 2: Logistic regression model adjusting for confounding factors of antipyretic therapy.

Variables	OR	Lower limit	Upper limit	p
Age	1.01	1.01	1.02	<0.001
SAPS-1	1.07	1.05	1.08	<0.001
SOFA	1.13	1.11	1.15	<0.001
Female versus male	1.05	0.93	1.19	0.438
Care unit (versus MICU as reference)				
SICU	0.66	0.50	0.86	0.003
CCU	0.92	0.78	1.07	0.273
CSRU	0.39	0.33	0.45	<0.001
Antipyretic therapy (any)	1.41	1.20	1.66	<0.001

OR, odds ratio; SAPS-1, Simplified Acute Physiology Score-1; SOFA, Sequential Organ Failure Assessment; MICU, medical intensive care unit; SICU, surgical intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery unit.

assume that the impact of antipyretic therapy on mortality for patients with different SOFA scores is quite small.

Figure 2 shows the plot of jittered outcome to reflect the relationship between age and probability of death. Probability of death was plotted on the y-axis for the fitted model and age on the x-axis. The classification of the model appears good in that most survivors have an estimated probability of death less than 0.2. As shown in the figure, there was no obvious change, but there was a statistically significant difference between age and probability of death. Therefore, we assume that the impact of antipyretic therapy on mortality for patients of different ages is quite small.

Figure 3 shows the nomogram for prediction of the risk of death for ICU patients with sepsis. Each variable was represented by a bar. A given value of a variable can be mapped to the point bar at the top of the graph and there is a point value for that given value. After each variable is assigned a point number, they are summed and mapped to the total point bar. Then there will be a value in the "risk of death" bar corresponding to those total points. For instance, you have a septic patient aged 50 (point = 29), with SAPSI of 25 (point = 48), SOFA of 12 (point = 50), from MICU (point = 55), and treated with antipyretic therapy (point = 13). The total points approximate 29 + 48 + 50 + 55 + 13 = 195, which corresponds to 54% probability of death.

4. Discussion

Evaluation of patient status before ICU admission is essential to ensure proper interventions and management of hospital resources. Variables including SOFA score, age, SAPS-1, lactate level, care unit type, and sex were crucial for the evaluation. Fever is common in septic ICU patients who receive mechanical ventilation treatment, so the protocol for fever control is vital to critically ill patients.

Our study indicated that antipyretic therapy had an adverse impact on mortality in critically ill patients with sepsis receiving mechanical ventilation treatment. We found that antipyretic therapy was positively associated with mortality risk (OR: 1.41, 95% CI: 1.20–1.66, $p < 0.001$; Table 2). This

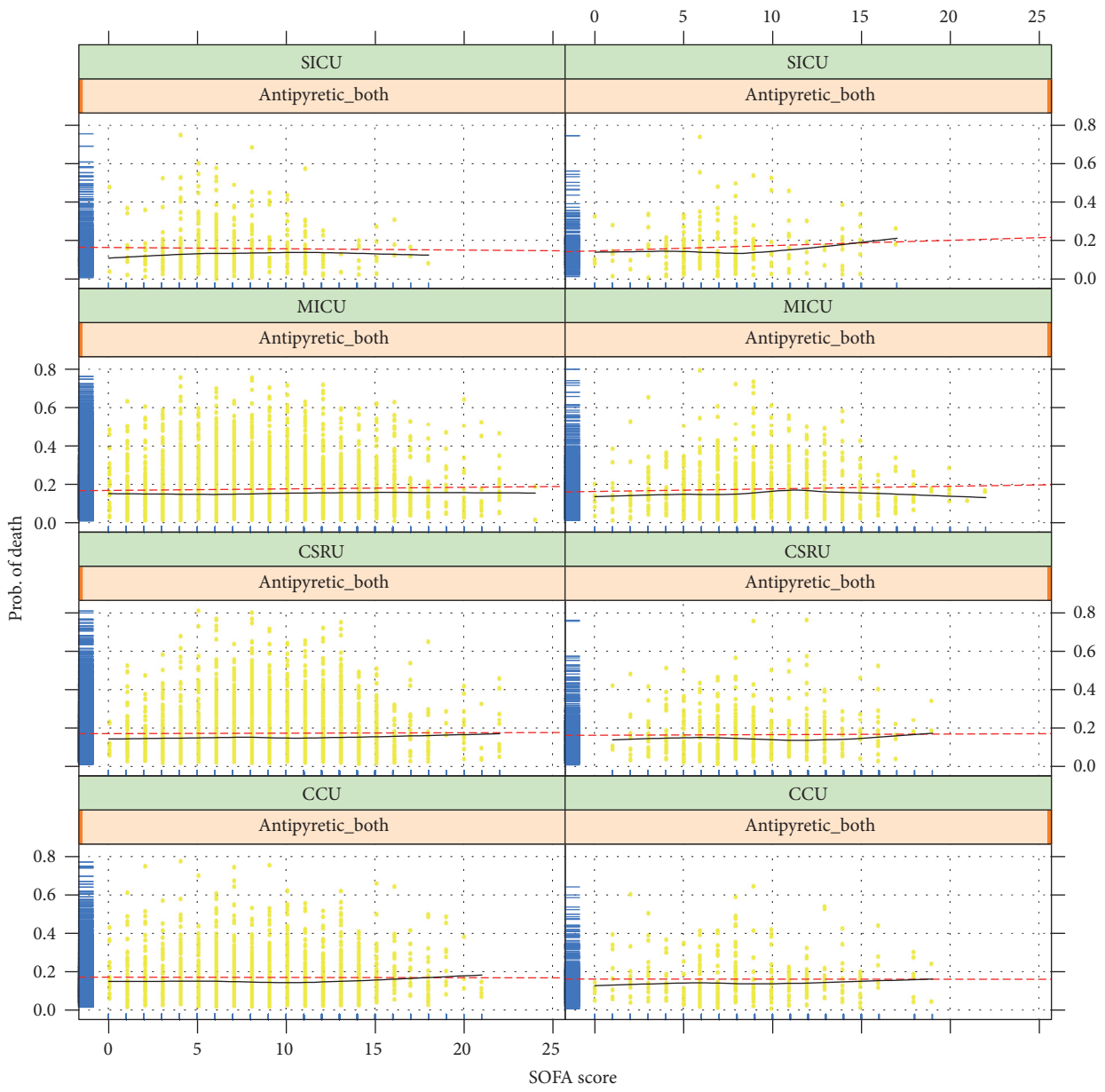


Figure 1

finding supports the hypothesis that hyperthermia is a natural response to infection and thus beneficial to septic patients who undergo mechanical ventilation treatment. It is plausible that the increased production of heat shock proteins, which are produced at the highest rate at high temperatures, could directly inhibit the growth of microorganisms and enhance immune function [20]. Some observational studies have shown that hyperthermia may confer protection against adverse outcome. In a study involving 612 patients with confirmed Gram-negative bacteria, fever within 24 hours was shown to be protective against mortality risk [21]. The FACE (Fever and Antipyretic in Critically Ill Patients Evaluation) investigators found that septic patients with a temperature above 39.5°C exhibited a downward trend in 28-day mortality [22]. A 2013 meta-analysis including 399 patients from five randomized trials found no survival benefit for antipyretic therapy in febrile critically ill patients (acute neurological injury excluded) [13], which is consistent with the results of our study. Randomized controlled trails are limited in sample size, which may lead to sampling error. Our study was based on data mining of critical care data, which can avoid the limitation of sample size.

As shown in Table 1, external cooling was associated with increased risk of death (13.5% versus 9.5%, $p < 0.001$), while there was no significant difference in the proportion of patients using antipyretic medications between survivors and nonsurvivors (7.9% versus 7.4%, $p = 0.49$). External cooling lowers the skin temperature and usually leads to muscle shivering, which can increase the metabolic rate, energy expenditure, and oxygen consumption. Therefore, external

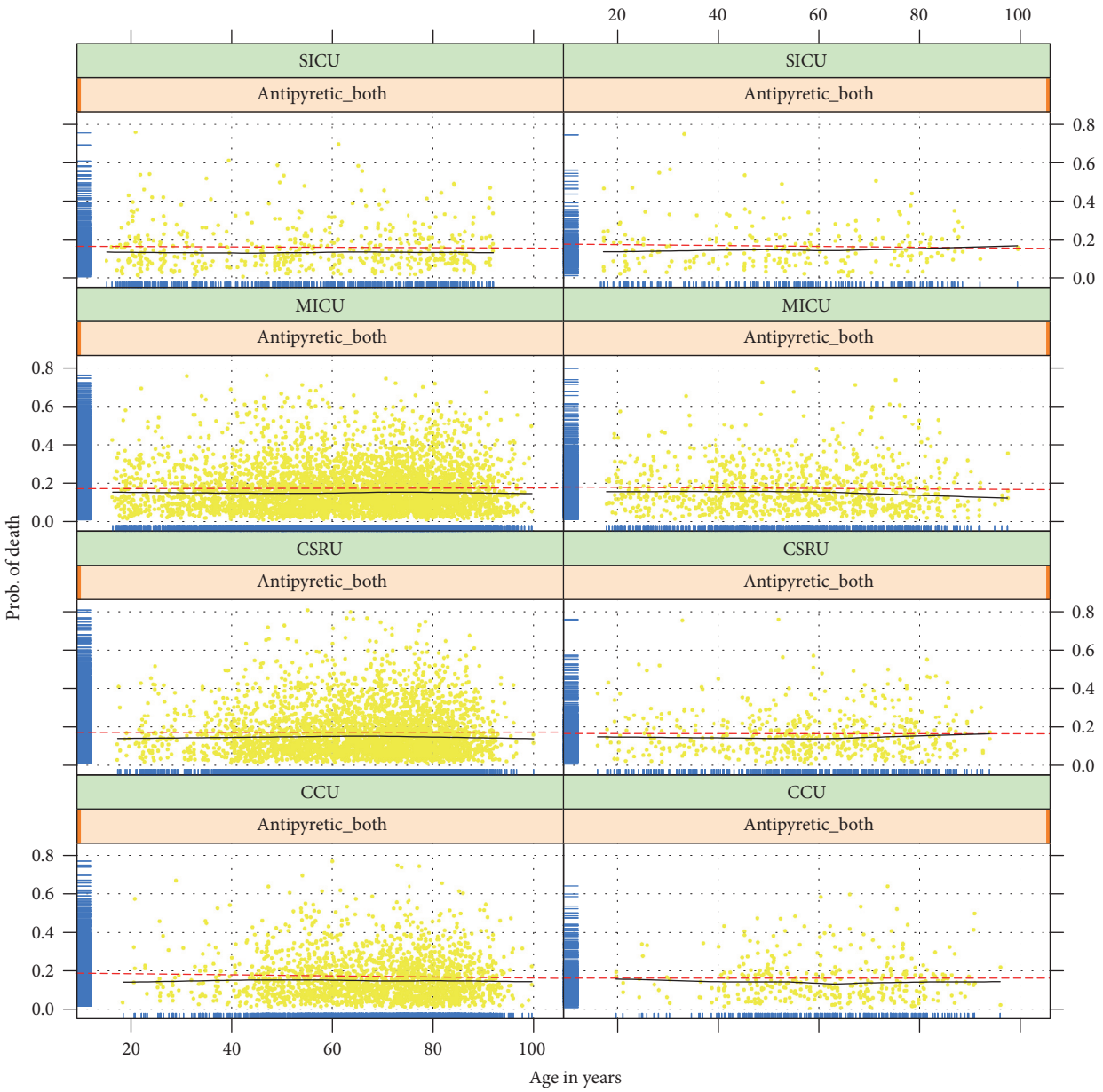


Figure 2

cooling tends to have greater adverse effects on mortality in critically ill patients with sepsis receiving mechanical ventilation compared to drug cooling, as shown in our study.

There were several limitations in the present study that should be acknowledged. The first one was that antipyretic therapy with drug and external cooling were combined in the multivariable analysis. In fact, the therapeutic effect of these two methods can be different. However, because some patients received both strategies for antipyretic treatment, it was difficult to disentangle the effects of these two treatments on mortality outcome. Further prospective trials may be conducted to investigate the specific effect of external cooling versus drug treatment.

Overall, our study found no beneficial effect of antipyretic therapy to reduce mortality risk in septic ICU patients requiring mechanical ventilation. External cooling may even be harmful. Since fever is very common in ventilated ICU patients with sepsis and antipyretic therapy may alter outcome, a large RCT comparing different fever control strategy in critically ill patients is urgently needed.

5. Conclusion

The use of antipyretic therapy is not beneficial for reducing mortality risk in septic ICU patients requiring mechanical ventilation. External cooling may even be deleterious.

Competing Interests

The authors declare that they have no competing interests.

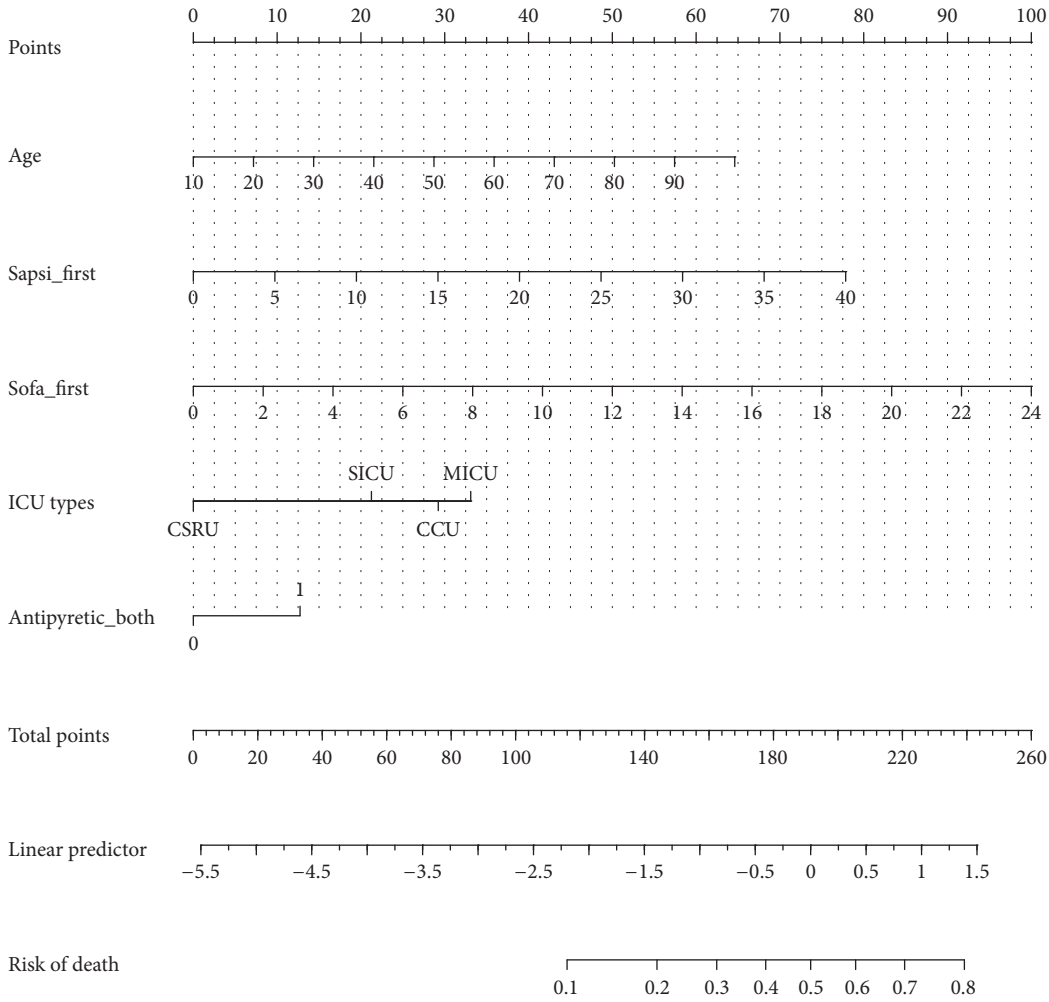


Figure 3: Figure nomogram.

Authors' Contributions

Yanyi Zhang and Dan Xu were responsible for data collection and management. Chenmei Zhang takes responsibility for the integrity of the work as a whole. Specific author contributions are as follows. Sheng Ye was responsible for study design, analysis, and interpretation of data. Drafting of the paper was done by Sheng Ye. Study supervision was the responsibility of Chenmei Zhang.

Acknowledgments

Sheng Ye has received grants from the Zhejiang Medical and Health Science and Technology Plan Project (2007 B119), the Zhejiang Medical and Health Science and Technology Plan Project (2012 KYB119), and the Natural Science Foundation of Zhejiang Province (LY12 H19006).

References

[1] D. McPherson, C. Griffiths, M. Williams et al., "Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010," *BMJ Open*, vol. 3, no. 8, Article ID e002586, 2013.

[2] J. E. Gotts and M. A. Matthay, "Sepsis: pathophysiology and clinical management," *BMJ (Online)*, vol. 353, Article ID i1585, 2016.

[3] J. Cavaillon, "Good and bad fever," *Critical Care*, vol. 16, no. 2, article no. 119, 2012.

[4] Y. Launey, N. Nesseler, Y. Mallédant, and P. Seguin, "Clinical review: fever in septic ICU patients—friend or foe?" *Critical Care*, vol. 15, article 222, 2011.

[5] "Estudio Nacional de Vigilancia de Infección Nosocomial en UCI (ENVIN-UCI) 2001–2009," 2012 http://hws.vhebron.net/envin-helics/.

[6] P. S. Barie, L. J. Hydo, and S. R. Eachempati, "Causes and consequences of fever complicating critical surgical illness," *Surgical Infections*, vol. 5, no. 2, pp. 145–159, 2004.

[7] J. R. Edwards, K. D. Peterson, Y. Mu et al., "National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009," *American Journal of Infection Control*, vol. 37, no. 10, pp. 783–805, 2009.

[8] P. M. Olaechea, J. Insausti, A. Blanco, and P. Luque, "Epidemiology and impact of nosocomial infections," *Medicina Intensiva*, vol. 34, no. 4, pp. 256–267, 2010.

[9] J. Beyersmann, T. Kneib, M. Schumacher, and P. Gastmeier, "Nosocomial infection, length of stay, and time-dependent bias," *Infection Control and Hospital Epidemiology*, vol. 30, no. 3, pp. 273–276, 2009.

[10] J. Chastre and J.-Y. Fagon, "Ventilator-associated pneumonia," *American Journal of Respiratory and Critical Care Medicine*, vol. 165, no. 7, pp. 867–903, 2002.

[11] J. G. Muscedere, A. Day, and D. K. Heyland, "Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and Hospital-acquired pneumonia," *Clinical Infectious Diseases*, vol. 51, no. 1, pp. S120–S125, 2010.

[12] M.-L. Lambert, C. Suetens, A. Savey et al., "Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study," *The Lancet Infectious Diseases*, vol. 11, no. 1, pp. 30–38, 2011.

[13] D. J. Niven, H. T. Stelfox, and K. B. Laupland, "Antipyretic therapy in febrile critically ill adults: a systematic review and meta-analysis," *Journal of Critical Care*, vol. 28, no. 3, pp. 303–310, 2013.

[14] Z. Zhang, L. Chen, and H. Ni, "Antipyretic therapy in critically ill patients with sepsis: an interaction with body temperature," *PLoS ONE*, vol. 10, no. 3, Article ID e0121919, 2015.

[15] J.-R. Gall, S. Lemeshow, and F. Saulnier, "A new simplified acute physiology score (SAPS II) based on a European/North American Multicenter Study," *JAMA: The Journal of the American Medical Association*, vol. 270, no. 24, pp. 2957–2963, 1993.

[16] J.-L. Vincent, R. Moreno, J. Takala et al., "The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure," *Intensive Care Medicine*, vol. 22, no. 7, pp. 707–710, 1996.

[17] J.-L. Vincent, A. De Mendonça, F. Cantraine et al., "Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study," *Critical Care Medicine*, vol. 26, no. 11, pp. 1793–1800, 1998.

[18] Z. Zhang, "Univariate description and bivariate statistical inference: the first step delving into data," *Annals of Translational Medicine*, vol. 4, no. 5, article 91, 2016.

[19] Z. Zhang, "Model building strategy for logistic regression: purposeful selection," *Annals of Translational Medicine*, vol. 4, no. 6, article 111, 2016.

[20] J. Bion, R. Jaeschke, B. T. Thompson, M. Levy, and R. P. Dellinger, "Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008," *Intensive Care Medicine*, vol. 34, no. 6, pp. 1163–1164, 2008.

[21] A. Jain, S. Palta, R. Saroa, A. Palta, S. Sama, and S. Gombar, "Sequential organ failure assessment scoring and prediction of patient's outcome in Intensive Care Unit of a tertiary care hospital," *Journal of Anaesthesiology Clinical Pharmacology*, vol. 32, no. 3, pp. 364–368, 2016.

[22] B. H. Lee, D. Inui, G. Y. Suh et al., "Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study," *Critical Care*, vol. 16, no. 1, article no. R33, 2012.

Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 7894631, 8 pages
https://doi.org/10.1155/2017/7894631

Clinical Study

Effect of High-Flow Nasal Cannula versus Conventional Oxygen Therapy for Patients with Thoracoscopic Lobectomy after Extubation

Yuetian Yu,[1] Xiaozhe Qian,[2] Chunyan Liu,[3] and Cheng Zhu[4]

[1]*Department of Critical Care Medicine, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China*
[2]*Department of Thoracic Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China*
[3]*Department of Emergency Medicine, Min Hang Central Hospital, School of Medicine, Fu Dan University, Shanghai, China*
[4]*Department of Emergency, Rui Jin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China*

Correspondence should be addressed to Cheng Zhu; zhucheng1203@163.com

Received 25 October 2016; Revised 11 December 2016; Accepted 22 January 2017; Published 19 February 2017

Academic Editor: Wan-Jie Gu

Objective. To investigate whether high-flow nasal cannula (HFNC) oxygen therapy is superior to conventional oxygen therapy for reducing hypoxemia and postoperative pulmonary complications (PPC) in patients with thoracoscopic lobectomy after extubation. *Methods*. Patients with intermediate to high risk for PPC were enrolled in this study. Subjects were randomly assigned to HFNC group (HFNCG) or conventional oxygen group (COG) following extubation. Arterial blood samples were collected after extubation at 1, 2, 6, 12, 24, 48, and 72 h. Patients with postoperative hypoxemia and PPC were recorded. Adverse events were also documented. *Results*. Totally 110 patients were randomly assigned to HFNCG ($n = 56$) and COG ($n = 54$). The occurrence rate of hypoxemia in COG was twice more than that in HFNCG (29.62% versus 12.51%, $P < 0.05$) and PaO_2, PaO_2/FiO_2, and SaO_2/FiO_2 were significantly improved in HFNCG ($P < 0.05$) in the first 72 h following extubation. Respiratory rate and incidence of reintubation as well as needing noninvasive ventilation were also decreased in HFNCG ($P < 0.05$), whereas the incidence of pneumonia and atelectasis were similar ($P > 0.05$). Adverse effects as throat and nasal pain occurred more frequently in COG. *Conclusions*. HFNC application improves oxygenation and reduces the risk of reintubation following thoracoscopic lobectomy but cannot decrease the incidence of PPC.

1. Introduction

Postextubation respiratory failure following major surgery is common, and a substantial proportion of the patients requires prolonged mechanical ventilation and prolonged intensive care unit (ICU) or hospital stay. Postoperative pulmonary complications (PPC) such as hypercapnia, atelectasis, and pneumonia which increase mortality are particularly attributable to adverse prognosis in patients with thorax surgery specially with lobectomy [1].

Respiratory support and oxygen therapy after tracheal extubation are of major importance to prevent hypoxemia and subsequent respiratory failure or reintubation in patients under general anaesthesia operation. Although conventional oxygen therapy via nasal prongs or a facemask can supplement oxygen administration, in some of the patients specially those who have lobectomy it is ineffective in compensating for loss in lung volume or in maintaining gas exchange [2]. High-flow nasal cannula oxygen (HFNC) mainly delivers a flow-dependent positive airway pressure and improves oxygenation by increasing end-expiratory lung volume, which can provide a maximum flow of 60 L/min [3]. It is considered to have a number of physiological advantages compared with other standard oxygen therapies, including the provision of positive end-expiratory pressure (PEEP), constant FiO_2, and good humidification. More importantly, it can reduce the anatomical dead space [4].

A few studies comparing HFNC and conventional oxygen therapy in patients with cardiac or abdominal surgery have been published in the last five years. However, the results remained controversial due to sample heterogeneity and there was no study reported in lobectomy patients.

We therefore hypothesized that HFNC treatment might be superior to conventional oxygen therapy in reducing the incidence of hypoxemia and PPC for patients with lobectomy after extubation.

2. Methods

2.1. Research Briefs. The present study was a multicenter (total of 155 ICU beds from three teaching hospitals) prospective interventional trial which was approved by the Review Board and Ethics Committee of Shanghai Jiaotong University School of Medicine (number: 2015-Clinical-Res-005). The study was unblinded and noncrossover. Informed consent was obtained for all patients, either from the patient or from the next of kin. The study took place from January 2015 to June 2016. One month before the start of this study, a standardized weaning protocol and statistics procedure were set by 9 investigators from these centers after 2 days' learning and discussion. All of the centers carefully followed this procedure during the study time.

2.2. Study Population. Consecutive sampling was used to recruit the patients who underwent planned thoracoscopic lobectomy because of lung tumor. Patients with intermediate to high risk for postoperative pulmonary complications (PPC) were eligible for participation. To identify such patients, the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score was used (Supplement 1 in Supplementary Material, available online at https://doi.org/10.1155/2017/7894631). ARISCAT score $\geq$ 26 is associated with an intermediate to high risk for PPC [5, 6]. Patients were excluded from the study if they were immunocompromised; were pregnant; converted to an open thoracotomy because of poor visualization or bleeding; or were aged <18 or >80 years or if informed consent could not be obtained.

2.3. Randomization, Intervention, and Weaning Protocol. All the patients eligible were transferred to ICU for postoperative monitoring and ventilator weaning at the end of the thoracoscopic lobectomy procedure. Patients were classified into two groups by random figure table following extubation. A random number sequence was generated with STATA statistical software version 12.1. HFNC oxygen therapy group (HFNCG) received a flow rate of 35 to 60 L/min and FiO_2 was titrated (from 45% to 100%) by the treating clinician to maintain a peripheral oxygen saturation (SpO_2) of 95% or more. The conventional oxygen therapy group (COG) received oxygen via either nasal prongs or facemask with oxygen flow titrated (from 45% to 100%) by the bedside clinician to maintain a SpO_2 of 95% or more. HFNC oxygen therapy was delivered by the Optiflow™ system (Fisher & Paykel Healthcare Ltd, Auckland, New Zealand) using a MR850 heated humidifier and a RT202 breathing circuit. Natural air includes about 21% oxygen. If a patient is wearing a nasal cannula or a simple facemask, each additional liter/min of oxygen adds about 4 percentage points for the first 3 liters and only 3 percentage points for every liter thereafter to their FiO_2.

Following the guideline of Difficult Airway Society Extubation Guidelines Group [7], the patients were ready for scheduled extubation after tolerating a spontaneous breathing trial in ICU. The decision to extubate was at the discretion of the treating doctors in ICU and no mandatory extubation variables were set.

2.4. Clinical Assessment and Outcomes. Baseline assessment included the evaluation of age, gender, body mass index (BMI), acute physiology and chronic health evaluation (APACHE) II score, ARISCAT score, baseline PaO_2, arterial oxygen tension to inspiratory oxygen fraction ratio (PaO_2/FiO_2), oxygen saturation to FiO_2 ratio (SaO_2/FiO_2), and $PaCO_2$ before operation. Asthma, chronic obstructive pulmonary disease (COPD), and smoke history were also recorded. Lung function before operation was measured as well and the value of functional residual capacity (FRC) and forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) were recorded.

The incidence of hypoxemia (defined as PaO_2/FiO_2 of 300 mmHg or less [8]) was recorded in the first 72 h after extubation and the differences of PaO_2, PaO_2/FiO_2, SaO_2/FiO_2, and $PaCO_2$ between the two groups were compared. Secondly, the rates of PPC like suspected pneumonia (patient receives antibiotics and meets at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest X-ray when clinically indicated, tympanic temperature >38.3°C, and white blood cell (WBC) count >12 $*$ 10^9/L in the absence of other infectious focus) and atelectasis (opacification of the lung with shift of the mediastinum, hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent nonatelectatic lung) [5] were also documented. Acute hypoxemic respiratory failure was defined by one of the hypoxemic criteria (SpO_2 < 92% while breathing at least 10 L/min oxygen, PaO_2 < 60 mmHg on air or PaO_2 < 80 mmHg while breathing any supplemental oxygen) and at least one of the following: severe respiratory distress with dyspnoea, accessory muscle recruitment and paradoxical abdominal or thoracic motion, respiratory rate >25 breaths/min, respiratory acidosis with pH < 7.30, and arterial carbon dioxide partial pressure ($PaCO_2$) >50 mmHg [8]. Once a patient after extubation was found with acute hypoxemic respiratory failure, noninvasive ventilation (NIV) (Bipap Vision with humidification, Respironics Inc, USA) was adopted. If the symptoms of respiratory distress did not improve within 2 hours, then reintubation might be considered. The incidence of NIV requirement and reintubation were also compared.

Adverse effects related to HFNC application and oxygen therapy (air leak, throat or nasal pain, and abdominal distension) were also recorded. As the previous studies indicated that it was with high incidence of PPC within 72 h following thoracoscopic lobectomy [1, 9], the arterial blood gases were consecutively collected and checked at 1, 2, 6, 12, 24, 48, and 72 h after extubation.

2.5. Statistical Analysis. Review of data from the three study centers over a 3-year period (2012~2014) revealed about 30%

Table 1: Demographic characteristics of the patients who participated in the study (mean ± SD).

Characteristics	HFNCG ($n = 56$)	COG ($n = 54$)	P
Age, yrs	56.31 ± 7.03	55.82 ± 7.92	0.732
Male gender, n (%)	30 (53.57)	28 (51.85)	1.000
BMI, kg/m^2	26.32 ± 4.73	25.19 ± 5.02	0.226
APACHE II	26.32 ± 4.73	25.19 ± 5.02	0.226
ARISCAT	31.12 ± 3.74	32.36 ± 3.08	0.071
COPD, n (%)	8 (14.29)	7 (12.96)	0.840
Asthma, n (%)	5 (8.93)	4 (7.41)	1.000
Smoking history, n (%)	12 (21.43)	8 (14.81)	0.369
Hemoglobin, g/L	108.29 ± 17.31	105.43 ± 22.06	0.450
Lactate, mmol/L	0.32 ± 0.07	0.33 ± 0.06	0.424
Respiratory, /min	18.43 ± 3.45	17.98 ± 3.87	0.521
PaO_2, mmHg	95.37 ± 12.42	92.59 ± 18.49	0.355
$PaCO_2$, mmHg	41.73 ± 6.33	43.52 ± 4.93	0.102
PaO_2/FiO_2, mmHg	350.35 ± 33.87	340.98 ± 40.65	0.191
SaO_2/FiO_2	210.37 ± 52.77	222.51 ± 48.65	0.213
FRC, L	2.08 ± 0.32	2.12 ± 0.41	0.567
FEV1/FVC, %	78.63 ± 11.52	75.52 ± 13.45	0.195
Postsurgical ventilation durations, h	2.13 ± 0.43	2.18 ± 0.32	0.492

of patients with hypoxemia who underwent thoracoscopic lobectomy after extubation. A sample size of 117 for each group provided 80% power to detect a reduction in hypoxemia from 30% to 15% (alpha = 0.05).

Statistical analysis was performed using SPSS version 19.0. Data were initially assessed for normality and were subject to log-transformation where appropriate [10]. Data between the HFNCG and COG were compared using Chi-square test for equal proportion or Fisher exact test where numbers were small with results presented as the number and percentage. Continuous variables with normal distribution were compared using Student's t-test and presented as means (standard deviations), whereas skewed data was compared using Wilcoxon rank-sum test and reported as medians (interquartile range). Two-way analysis of variance (ANOVA) for repeated measures with Bonferroni post hoc analysis was used for analysis of the modification of variables over time in the two groups. All analyses were performed on an intention-to-treat basis and a two-sided $P < 0.05$ was considered to be statistically significant. Figures were drawn using Graphpad prism version 6.0.

3. Results

3.1. Characteristics of the Patients. Over the study period, a total of 141 patients were screened and 110 eligible patients were recruited for the study. A total of 56 patients were assigned to HFNCG and 54 patients to COG. Thirty-one patients who met the exclusion criteria were excluded from the study. All patients included were followed until discharge home (Figure 1). The baseline characteristics of the 110 eligible patients are shown in Table 1. There were no significant differences between patients in two groups in all aspects ($P > 0.05$). Lung squamous cell carcinoma was the most prevalent type in both groups (57.14% versus 59.26%, $P > 0.05$).

3.2. Outcomes Comparison. Although lung tumor was removed by thoracoscopic surgery in a relatively less invasive way, the incidence of hypoxemia was still high during the study period due to the high risk of the patients included. The occurrence rate of hypoxemia in COG was 29.62%, two times more than that in HFNCG (12.51%), $P < 0.05$. The rate of needing NIV was still high in COG as well as the rate of reintubation ($P < 0.05$). There was no significant difference in the rate of hypercapnia, atelectasis, and suspected pneumonia (Table 2).

Because there were two different oxygen supplement strategies (via prongs or facemask) in COG, the outcomes between nasal prongs and facemask patients were also compared. It was indicated that different ways of oxygen therapy in COG did not affect the outcomes 72 h following extubation ($P > 0.05$) (Table 3). Because all subjects included in our study had intermediate to high risk for PPC, different oxygen concentrations were supplied following extubation. It revealed that hypoxemia, reintubation, and needing NIV were more likely to occur in higher oxygen concentrations patients in COG ($P < 0.05$) while there was no difference in HFNCG ($P > 0.05$) (Table 4).

We also found that there was no difference in mortality, length of ICU stay, and length of hospital stay between the two groups ($P > 0.05$). However, the total hospitalization expenditures in COG was higher than that in HFNCG (Table 5).

According to ANOVA for repeated measures, the values of $PaCO_2$ and lactate were similar within the two groups throughout the entire study period in all time points ($P >$

Table 2: Occurrence rates for outcomes in COG compared with HFNCG 72 h following extubation, *n* (%).

Characteristics	HFNCG ($n = 56$)	COG ($n = 54$)	P
Hypoxemia	7 (12.50)	16 (29.63)	0.027
Hypercapnia	3 (5.36)	8 (14.81)	0.121
Reintubation	0 (0)	5 (9.26)	0.026
Needing NIV	2 (3.57)	9 (16.67)	0.027
Atelectasis	2 (3.57)	5 (9.26)	0.266
Suspected pneumonia	2 (3.57)	2 (3.70)	1.000
Throat or nasal pain	1 (1.79)	7 (12.96)	0.030
Abdominal distension	3 (5.36)	0 (0)	0.243
Air leak	0 (0)	0 (0)	1.000

Table 3: Occurrence rates for outcomes in nasal prongs patients compared with facemask patients 72 h following extubation, *n* (%).

Characteristics	Nasal prongs ($n = 29$)	Facemask ($n = 25$)	P
Hypoxemia	9 (31.03)	7 (28.00)	0.808
Hypercapnia	4 (13.79)	4 (16.00)	1.000
Reintubation	3 (10.34)	2 (8.00)	1.000
Needing NIV	4 (13.79)	5 (20.00)	0.718
Atelectasis	2 (6.89)	3 (12.00)	0.653
Suspected pneumonia	1 (3.45)	1 (4.00)	1.000
Throat or nasal pain	3 (10.34)	4 (16.00)	0.692
Abdominal distension	0 (0)	0 (0)	1.000
Air leak	0 (0)	0 (0)	1.000

0.05). PaO_2 values were higher in the HFNC group at all time points, respectively ($P < 0.05$), as well as the PaO_2/FiO_2 ratio and SaO_2/FiO_2 ratio. We also found that the respiratory rate in HFNC was not that high in COG during the 72 h after extubation (Figure 2).

3.3. Adverse Effects Comparison. In three patients in HFNCG abdominal distension occurred during the time of oxygen therapy but the HFNC therapy could still be continued, while there was none in COG. Throat or nasal pain seems to have a high morbidity in COG (12.96%) for lack of proper humidity. No other adverse effects related to oxygen therapy, such as nasal trauma or intolerance of the therapy, need for supplemental sedation, and air leak, were found during our study period (Table 5).

4. Discussion

In this multicenter randomized interventional trial, we found that the application of HFNC oxygen therapy in patients with thoracoscopic lobectomy after extubation could reduce the risk of hypoxemia and reintubation as well as improve oxygenation represented by PaO_2, PaO_2/FiO_2, and SaO_2/FiO_2. Despite extensive physiological data, there are few data on the use of HFNC in preventing the worsening of respiratory function following lobectomy. To the best of our knowledge, this study is the first randomized, controlled trial exploring the use of HFNC in adult thoracoscopic lobectomy patients.

HFNC is widely employed for patients of all age groups in several types of respiratory failure from preterm infants to adults [11] and is broadly used in ICU because of the ease of use, tolerability, and safety [3]. It has been reported to improve oxygenation after extubation in infants [12]. One clinical study indicated that HFNC might have benefit in patients with abdominal surgery [13]. However, after two years of research, they failed to identify beneficial effect of HFNC therapy after extubation in terms of the reduction of either reintubation or NIV application. Another multicenter randomized clinical trial showed that, in low risk patients, HFNC reduced the risk of reintubation within 72 hours [14]. Collectively, current literature cannot provide definitive evidence on whether HFNC treatment is superior to conventional oxygen therapy. Among the reasons, the most important factor was that patients involved in these studies were mixed populations which leaded to high heterogeneity. In our study, only patients with thoracoscopic lobectomy following extubation were included, which reduced the heterogeneity of sample and avoided misinterpreting the results.

One observational trial by Sztrymf et al. [15] demonstrated that HFNC was associated with significant reductions in respiratory rate and thoracoabdominal asynchrony and a significant improvement in arterial oxygen saturation. Our findings are consistent with this study. In the first 72 h after extubation, respiratory rate in HFNCG was lower than that in COG at any time point. The total medical costs in COG were much higher. In our opinion, relatively more NIV and reintubation in COG may help to explain the increased medical costs, since either reintubation or NIV application will prolong ICU and hospital stay. However, we could not reach the conclusion in our study. First of all, the percentage

Table 4: Occurrence rates for outcomes in HFNC patients compared with COG patients with different oxygen concentrations 72 h following extubation, *n* (%).

Characteristics	HFNCG ($n = 56$)			P	COG ($n = 54$)			P
	FiO_2 (45~60%) ($n = 18$)	FiO_2 (60~80%) ($n = 22$)	FiO_2 (80~100%) ($n = 16$)		FiO_2 (45~60%) ($n = 17$)	FiO_2 (60~80%) ($n = 21$)	FiO_2 (80~100%) ($n = 16$)	
Hypoxemia	2 (11.11)	2 (9.09)	3 (18.75)	0.658	2 (11.76)	5 (23.81)	9 (56.25)	0.015
Hypercapnia	1 (5.56)	1 (4.55)	1 (6.25)	0.973	2 (11.76)	4 (19.05)	2 (12.50)	0.782
Reintubation	0 (0)	0 (0)	0 (0)	1.000	0 (0)	1 (4.76)	4 (25.00)	0.031
Needing NIV	0 (0)	0 (0)	2 (12.5)	0.075	0 (0)	3 (14.29)	6 (37.50)	0.014
Atelectasis	1 (5.56)	0 (0)	1 (6.25)	0.508	1 (5.88)	2 (9.52)	2 (12.50)	0.806
Suspected pneumonia	0 (0)	1 (4.55)	1 (6.25)	0.588	0 (0)	1 (4.76)	1 (6.25)	0.603
Throat or nasal pain	0 (0)	1 (4.55)	0 (0)	0.455	0 (0)	2 (9.52)	5 (31.25)	0.024
Abdominal distension	0 (0)	0 (0)	3 (18.75)	0.019	0 (0)	0 (0)	0 (0)	1.000
Air leak	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000

Table 5: Comparison of hospitalizations between two groups (mean ± SD).

Characteristics	HFNCG ($n = 56$)	COG ($n = 54$)	P
Mortality	0	0	1.000
Length of ICU stay, days	3.72 ± 0.56	3.64 ± 0.83	0.553
Length of hospital stay, days	7.41 ± 0.82	7.54 ± 0.91	0.433
Total hospitalization expenditures, $	11522.65 ± 762.45	12219.73 ± 1028.66	0.001

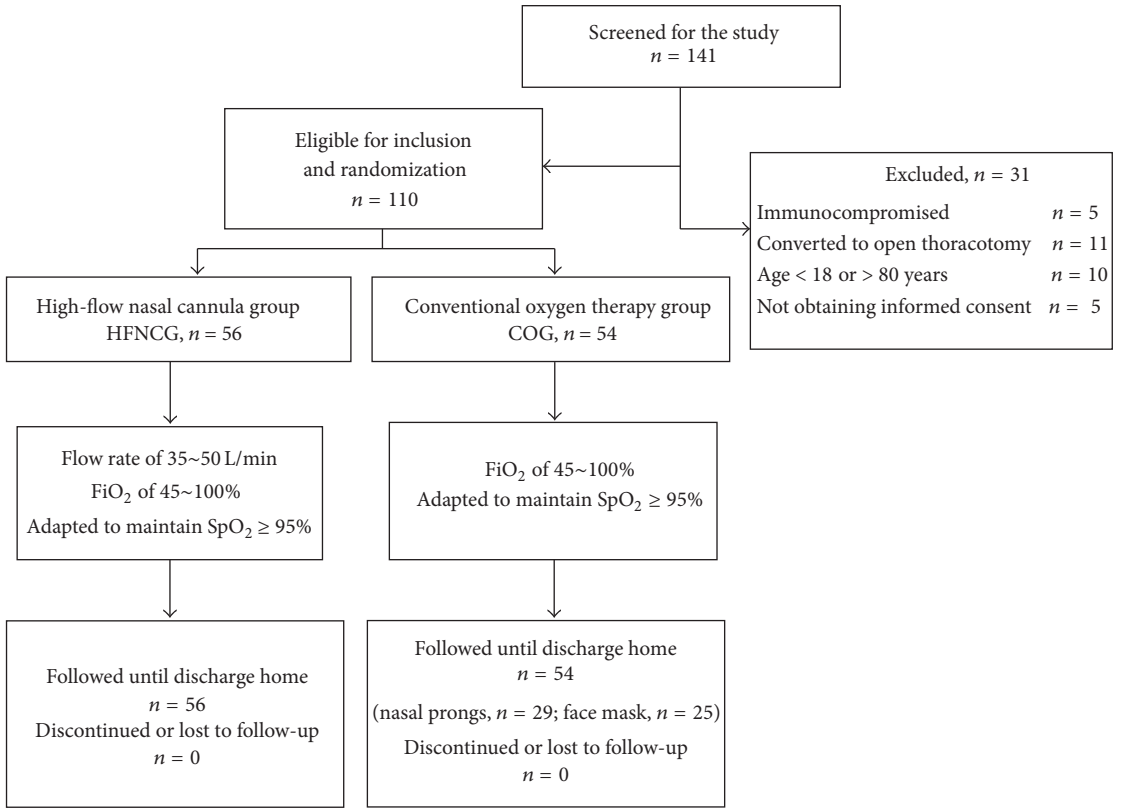


Figure 1: Flow chart of the study.

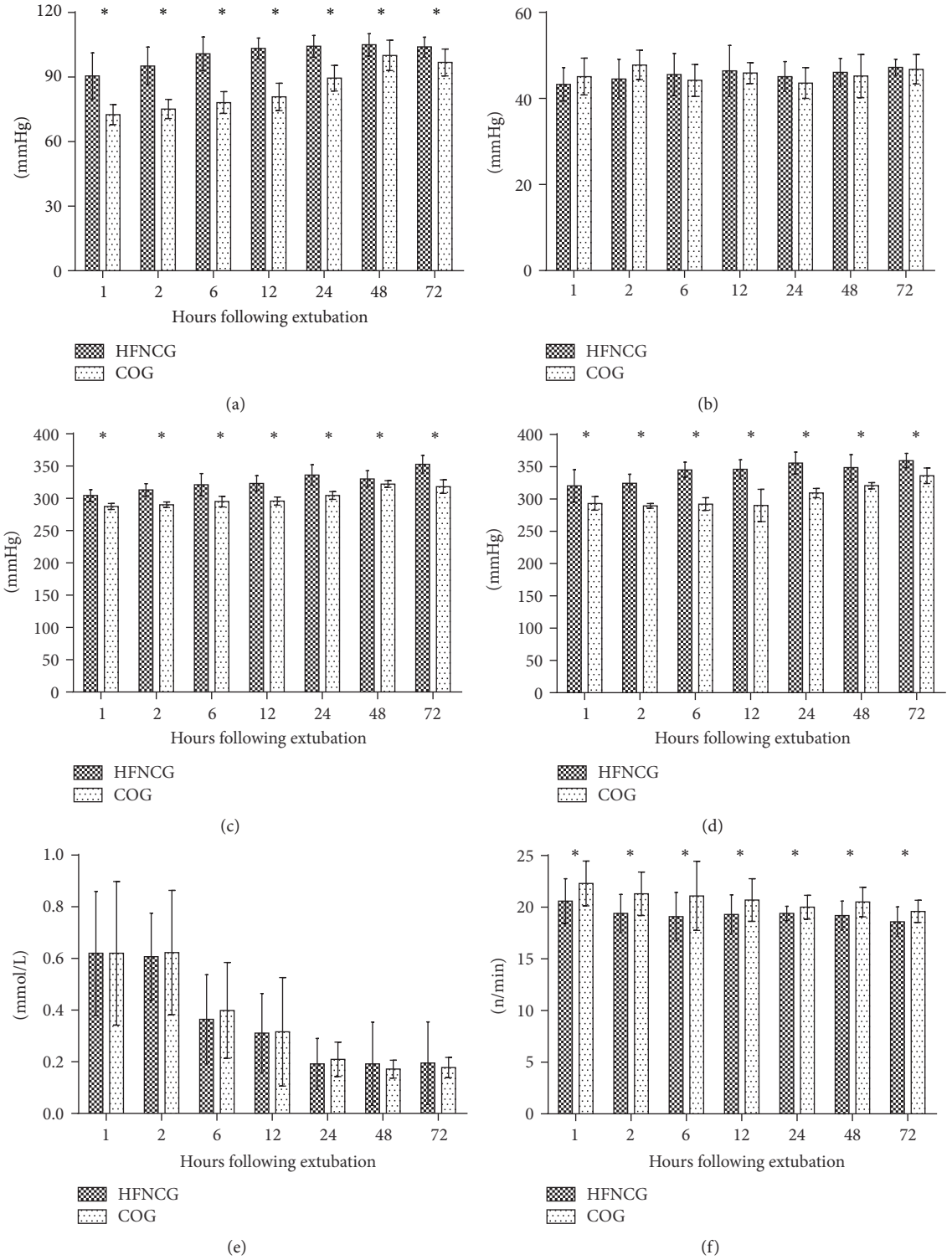


FIGURE 2: Comparison of variables between two groups in different time points. (a) Arterial PaO_2 values; (b) arterial $PaCO_2$ values; (c) the PaO_2/fractional inspired oxygen (FiO_2) ratio; (d) oxygen saturation/FiO_2 ratio; (e) lactate values; (f) respiratory rate. $^*P < 0.05$.

of patients with COPD or asthma was relatively low in both of the two groups (<15%), leading to a short duration of NIV usage (less than 3 days). Secondly, we acknowledged that a comparatively small sample size in our study might compromise the statistical power of the study.

In our study, the patients enrolled were those who underwent lobectomy and the occurrence of hypoxemia in HFNCG was relatively lower than that in COG, as well as the rate of needing NIV and the rate of reintubation ($P < 0.05$) which reflected the advantage of HFNC.

Although several approaches for providing supplemental oxygen have been suggested, the best option for patients with postoperation extubation remains unclear. HFNC delivers some level of continuous positive airway pressure (CPAP) via high-flow ventilation. However, the value of CPAP is unstable (from 1 to 7 cm H_2O) because of the leak around the nasal cannula and a closed mouth of the patients cannot always be guaranteed [16]. Due to the provision of distending pressure and increase in end-expiratory lung volume, some researchers proposed that it decreased airway resistance and flushed nasopharyngeal dead space, thereby contributing to the reduced work of breathing [17, 18]. Considering the suspected induced effects of HFNC on lung volumes [19], we hypothesized that early initiation of HFNC could minimize in part lung derecruitment after extubation. Itagaki et al. reported better thoracoabdominal synchrony, measured using respiratory inductance plethysmography, in patients with mild to moderate respiratory failure when comparing high-flow nasal cannulas to standard oxygen therapy [20]. In this respect, our results support the findings of previous studies [21, 22], which suggest that HFNC oxygen therapy may favorably decrease the respiratory rate both in infants and in adult patients.

Several studies [17, 20] have demonstrated that HFNC could accelerate the elimination of CO_2 and bronchial secretions which indicated that it might decrease the incidence of hypercapnia and pneumonia. Accordingly, we speculated that the increased flow of HFNC was able to reduce the work of breathing by flushing the nasopharyngeal space and improve CO_2 elimination after extubation after lobectomy. However, there was no difference in the incidence of hypercapnia and pneumonia between the groups in our study which was due to few patients with severe COPD or with muscle fatigue who were included in study period.

Dry or poorly humidified medical gas may elicit patient complaints, such as dry nose, dry throat, and nasal pain, and consequent poor tolerance of oxygen therapy. Better patient comfort, a reduction in respiratory rate with a similar arterial carbon dioxide, and a higher oxygenation were reported during high-flow nasal cannula support in Roca et al.'s study [23]. However, abdominal distension which was a major complication caused by HFNC in our study is a problem that cannot be ignored. HFNC is an open ventilation system, yet it is still able to increase end-expiratory pressure. Pharyngeal pressure is affected by mouth-opening or closing, delivered flow, and size of nasal prongs. Usually, pharyngeal pressure is less than 5 cm H_2O; however, pressure is not predictable or sustained, so we shall apply HFNC with caution in gastrointestinal surgery patients. In addition, with high flow there is an increase in the airway pressure which may make the population of our study at risk of air leak following thoracic surgery. During the study period, no patients of air leak were reported due to the pressure generated by HFNC being relatively low.

4.1. Study Limitation. We acknowledge that there are limitations in the study. We calculated the sample size by using a historical review of extubation data from 2012 to 2014 before the study initiated. The sample size expected in each group was 117. However, during our 18-month (January 2015 to June 2016) study period, the patients eligible were not as much as we expected because the majority of patients with lobectomy were at low risk which might have been attributable to overall improvements in perioperative surgical care. This might lead to compromised statistical power to detect a significant difference between groups in the primary outcome. In addition, postoperative changes in pulmonary function were not recorded and compared. Anyway, our study did show a clear clinical benefit of high-flow nasal cannula oxygen therapy.

4.2. Conclusion. HFNC application improves oxygenation and reduces the risk of reintubation. It should be used as an alternative to the conventional oxygen therapy especially for patients receiving thoracoscopic lobectomy following extubation.

Abbreviations

APACHE: Acute physiology and chronic health evaluation
ARISCAT: Assess Respiratory Risk in Surgical Patients in Catalonia
BMI: Body mass index
COPD: Chronic obstructive pulmonary disease
CPAP: Continuous positive airway pressure
FEV1: Forced expiratory volume in one second
FRC: Functional residual capacity
FVC: Forced vital capacity
HFNC: High-flow nasal cannula oxygen
ICU: Intensive care unit
NIV: Noninvasive ventilation
PEEP: Positive end-expiratory pressure
PPC: Postoperative pulmonary complications.

Competing Interests

The authors have declared that no competing interests exist.

Authors' Contributions

Yuetian Yu and Cheng Zhu both helped in drafting and editing the article. Chunyan Liu revised the language of the manuscript. Xiaozhe Qian and Cheng Zhu revised and approved the final manuscript. Yuetian Yu and Xiaozhe Qian contributed equally to this work.

References

[1] C.-C. Tu and P.-K. Hsu, "Global development and current evidence of uniportal thoracoscopic surgery," *Journal of Thoracic Disease*, vol. 8, pp. S308–S318, 2016.

[2] M. Licker, M. De Perrot, A. Spiliopoulos et al., "Risk factors for acute lung injury after thoracic surgery for lung cancer," *Anesthesia and Analgesia*, vol. 97, no. 6, pp. 1558–1565, 2003.

[3] L. Papazian, A. Corley, D. Hess et al., "Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review," *Intensive Care Medicine*, vol. 42, no. 9, pp. 1336–1349, 2016.

[4] M. Nishimura, "High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects," *Respiratory Care*, vol. 61, no. 4, pp. 529–541, 2016.

[5] V. Mazo, S. Sabaté, J. Canet et al., "Prospective external validation of a predictive score for postoperative pulmonary complications," *Anesthesiology*, vol. 121, no. 2, pp. 219–231, 2014.

[6] J. Canet, L. Gallart, C. Gomar et al., "Prediction of postoperative pulmonary complications in a population-based surgical cohort," *Anesthesiology*, vol. 113, no. 6, pp. 1338–1350, 2010.

[7] M. Popat, V. Mitchell, R. Dravid, A. Patel, C. Swampillai, and A. Higgs, "Difficult Airway Society Guidelines for the management of tracheal extubation," *Anaesthesia*, vol. 67, no. 3, pp. 318–340, 2012.

[8] J. G. Toffaletti and C. R. Rackley, "Monitoring oxygen status," *Advances in Clinical Chemistry*, vol. 77, pp. 103–124, 2016.

[9] T. Kammerer, E. Speck, and V. von Dossow, "Anesthesia in thoracic surgery," *Anaesthesist*, vol. 65, no. 5, pp. 397–412, 2016.

[10] Z. Zhang, "Univariate description and bivariate statistical inference: the first step delving into data," *Annals of Translational Medicine*, vol. 4, no. 5, article no. 91, 2016.

[11] J. H. Lee, K. J. Rehder, L. Williford, I. M. Cheifetz, and D. A. Turner, "Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature," *Intensive Care Medicine*, vol. 39, no. 2, pp. 247–257, 2013.

[12] C. L. Collins, J. R. Holberton, C. Barfield, and P. G. Davis, "A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants," *Journal of Pediatrics*, vol. 162, no. 5, pp. 949.e1–954.e1, 2013.

[13] E. Futier, C. Paugam-Burtz, T. Godet et al., "Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA)," *Intensive Care Medicine*, vol. 42, no. 12, pp. 1888–1898, 2016.

[14] G. Hernández, C. Vaquero, P. González et al., "Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial," *JAMA*, vol. 315, no. 13, pp. 1354–1361, 2016.

[15] B. Sztrymf, J. Messika, F. Bertrand et al., "Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study," *Intensive Care Medicine*, vol. 37, no. 11, pp. 1780–1786, 2011.

[16] Z. J. Kubicka, J. Limauro, and R. A. Darnall, "Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure?" *Pediatrics*, vol. 121, no. 1, pp. 82–88, 2008.

[17] G. Testa, F. Iodice, Z. Ricci et al., "Comparative evaluation of high-flow nasal cannula and conventional oxygen therapy in paediatric cardiac surgical patients: a randomized controlled trial," *Interactive Cardiovascular and Thoracic Surgery*, vol. 19, no. 3, pp. 456–461, 2014.

[18] J. W. Shepard Jr. and C. D. Burger, "Nasal and oral flow-volume loops in normal subjects and patients with obstructive sleep apnea," *American Review of Respiratory Disease*, vol. 142, no. 6, part 1, pp. 1288–1293, 1990.

[19] G. Spoletini, M. Alotaibi, F. Blasi, and N. S. Hill, "Heated humidified high-flow nasal oxygen in adults: Mechanisms of action and clinical implications," *Chest*, vol. 148, no. 1, pp. 253–261, 2015.

[20] T. Itagaki, N. Okuda, Y. Tsunano et al., "Effect of high-flow nasal cannula on thoraco-abdominal synchrony in adult critically Ill patients," *Respiratory Care*, vol. 59, no. 1, pp. 70–74, 2014.

[21] A. Corley, L. R. Caruana, A. G. Barnett, O. Tronstad, and J. F. Fraser, "Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients," *British Journal of Anaesthesia*, vol. 107, no. 6, pp. 998–1004, 2011.

[22] J. Riera, P. Pérez, J. Cortés, O. Roca, J. R. Masclans, and J. Rello, "Effect of high-flow nasal cannula and body position on end-expiratory lung volume: A Cohort Study Using Electrical Impedance Tomography," *Respiratory Care*, vol. 58, no. 4, pp. 589–596, 2013.

[23] O. Roca, J. Riera, F. Torres, and J. R. Masclans, "High-flow oxygen therapy in acute respiratory failure," *Respiratory Care*, vol. 55, no. 4, pp. 408–413, 2010.

Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 2048032, 6 pages
https://doi.org/10.1155/2017/2048032

Clinical Study

Comparison of Comfort and Effectiveness of Total Face Mask and Oronasal Mask in Noninvasive Positive Pressure Ventilation in Patients with Acute Respiratory Failure: A Clinical Trial

Somayeh Sadeghi,[1] Atefeh Fakharian,[2] Peiman Nasri,[3] and Arda Kiani[4]

[1]*Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran*
[2]*Chronic Respiratory Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[3]*Department of Pediatric Gastroenterology and Hepatology, Emam Hosein Hospital, Isfahan University of Medical Sciences, Isfahan, Iran*
[4]*Tracheal Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Correspondence should be addressed to Atefeh Fakharian; fakharian_2005@yahoo.com

Received 17 August 2016; Revised 13 November 2016; Accepted 10 January 2017; Published 8 February 2017

Academic Editor: Zhongheng Zhang

Background. There is a growing controversy about the use of oronasal masks (ONM) or total facemask (TFM) in noninvasive positive pressure ventilation (NPPV), so we designed a trial to compare the uses of these two masks in terms of effectiveness and comfort. *Methods*. Between February and November 2014, a total of 48 patients with respiratory failure were studied. Patients were randomized to receive NPPV via ONM or TFM. Data were recorded at 60 minutes and six and 24 hours after intervention. Patient comfort was assessed using a questionnaire. Data were analyzed using t-test and chi-square test. Repeated measures ANOVA and Mann–Whitney U test were used to compare clinical and laboratory data. *Results*. There were no differences in venous blood gas (VBG) values between the two groups ($P > 0.05$). However, at six hours, TFM was much more effective in reducing the partial pressure of carbon dioxide (PCO2) ($P = 0.04$). Patient comfort and acceptance were statistically similar in both groups ($P > 0.05$). Total time of NPPV was also similar in the two groups ($P > 0.05$). *Conclusions*. TFM was superior to ONM in acute phase of respiratory failure but not once the patients were out of acute phase.

1. Introduction

Oronasal masks (ONM) have historically been the preferred choice in acute cases because of reduced air leak from the mouth, while nasal masks are preferred for prolonged ventilation as they do not cover the patient's mouth and provide more comfort [1, 2]. However, one-third of patients refuse both ONM and nasal masks due to air leak, face discomfort, and claustrophobia [3, 4]. There is a growing controversy about using ONM as the first choice in patients with acute respiratory failure [1, 2, 5] while total face mask (TFM) has been developed to improve patient compliance. While some authors reported better patient tolerance and reduced air leak in patients using TFM [6, 7], others have reported no difference between the two masks in terms of efficacy and outcome [7]. To date, there is no evidence supporting the clinical superiority of TFM in spite of its improved acceptance by the patients. Thus, this trial was designed to compare TFM and ONM in terms of effectiveness and comfort in patients with acute respiratory failure who were receiving noninvasive positive pressure ventilation (NPPV).

2. Materials and Methods

The study protocol was approved by the ethics committee of Masih Daneshvari Hospital and registered at http://www.irct.ir/ (IRCT2016051627929N1). This randomized controlled trial was conducted on 48 patients with acute respiratory failure who were referred to Masih Daneshvari Hospital from February to November of 2014. The diagnosis of acute respiratory failure was made based on medical history and thorough clinical examination. Patients were

enrolled if they showed at least one of the following signs: tachypnea (respiratory rate ≥ 24), use of accessory muscles of respiration (defined as contraction of sternocleidomastoid and intercostal, suprasternal, or supraclavicular retractions during inhalation), paradoxical respiration, pH < 7.35 with no metabolic component, and finally $PaCO_2$ > 45 mmHg while breathing room air. Patients with fluctuating mental status, unstable coronary artery disease, arrhythmias with unstable blood pressure (SBP ≤ 90 mm Hg or > 40 mmHg drop in systolic blood pressure), generalized skin lesions, facial trauma, upper airway obstruction, and recent surgery on upper airways, stomach, or esophagus and those who required emergent intubation were excluded. Six patients had problems with using the assigned masks due to previous unpleasant experiences or difficulties in adapting the mask to their face and consequently were excluded after randomization.

2.1. NPPV Technique. Patients with acute respiratory failure who were referred to Masih Daneshvari Hospital were divided into two groups, using simple randomization with a table of random numbers. Patients in the first group received NPPV through ONM (Respironics Amara® full face mask: Philips Respironics, United States) while the patients in the second group received NPPV via TFM (Respironics FitLife® mask SE: Philip Respironics, United States).

NPPV was delivered by trained personnel in Masih Daneshvari Hospital (ward and emergency room) under the supervision of pulmonary and critical care fellows. The patients played no role in selection of the mask and the statistician was blinded to the group allocation of patients. Ventilator (ResMed®Stellar 150: by Germany Inc. Fraunhoferstr, Germany) was used for all patients. NPPV parameters were set based on prior reports for 24 hours continuously. We started with inspiratory positive airway pressure (IPAP) of 10 and expiratory positive airway pressure (EPAP) of 4 cm H_2O. Based on the severity of disease and physical symptoms, IPAP and if necessary EPAP were gradually increased within the patient's level of tolerance each time for approximately 2 cm/H2O. The primary goal was to eliminate respiratory distress, decrease the respiratory rate, and decrease the use of accessory respiratory muscles. The second goal was to improve blood gases and particularly PCO2 and pH. Necessary adjustments to NPPV settings were made based on clinical criteria and venous blood gases (VBGs). Supplemental oxygen, 3–15 L/min, was utilized to achieve peripheral oxygen saturation rate of ≥ 90% while the mask was fitted on the patient's face to minimize air leak. Cardiac monitoring and pulse oximetry as well as noninvasive blood pressure measurements were performed continuously during NPPV, and ventilator parameters (IPAP and EPAP) were recorded.

2.2. Outcome Measures. Epidemiologic data such as age and sex in addition to clinical and laboratory data including blood pressure, pulse rate, respiratory rate, accessory respiratory muscle use, and SaO_2 and VBG parameters (HCO3, BE, PCO2, and pH) were measured at the time of enrollment and subsequently at 60 minutes and six and 24 hours after NPPV initiation. Support provided by the ventilator was quantified by measuring IPAP and EPAP, as well as total oxygen flow required to maintain peripheral oxygen saturation rate above 90%. Patient comfort while wearing the mask was assessed by two methods, namely, a visual analog scale (VAS) and a questionnaire. In use of a VAS, a score of 5 indicated that the patient was very comfortable while a score of 1 indicated extreme discomfort. Patients were asked about feeling pain in the forehead, nose, cheeks, and chin, air leak at eyes and mouth, dry nose and mouth, and compressive effects of mask on their faces. The patients' answers to the following questions were recorded in a questionnaire and each item was scored 0 to 3 in terms of intensity. The total score was calculated by adding the individual scores of each item mentioned above. Duration of NPPV use, endotracheal intubation rate, length of hospital stay, and in-hospital mortality rate were compared between the two groups as well.

2.3. Statistics. We used SPSS version 22 for statistical analysis. Data were analyzed using t-test and chi-square test considering 95% confidence interval, At $P = 0.05$ level of significance. Repeated measures ANOVA and Mann–Whitney U test were used to compare clinical and laboratory data between the two groups.

3. Results

The study was conducted between February and November 2014. There were no significant differences in age, sex, or disease severity ($P > 0.05$) in patients between the two groups. Patients in group one (13 men and 11 women) used TFM; 20 patients in this group (83.3%) had chronic obstructive pulmonary disease (COPD) exacerbations, while the rest had bronchiectasis, obstructive sleep apnea, and so forth. The mean age was 63.21 ± 10.22 years. Patients in group 2 (15 men and 9 women) used ONM. There were 20 patients with COPD exacerbation in this group, with a mean age of 67.83 ± 9.46 years. The demographics of the two groups are summarized in Table 1.

There was no difference in baseline heart rate of patients in the two groups. Similarly, there were no differences in respiratory rate, O_2 saturation, or the use of accessory respiratory muscles at baseline between the two groups (Table 2).

At 6 hours, the patients in the TFM group had a significant reduction in their respiratory rate compared to those in the ONM group ($P = 0.045$). Table 3 shows the recorded parameters at 1, 6, and 24 hours after initiation of NPPV in both groups.

As seen in Table 3, at six hours, PCO2 and HCO3 improved in patients using TFM, although there were no differences in VBG alterations between the two groups ($P > 0.055$).

With regard to patient comfort and acceptance, except for pain in the cheeks ($P = 0.01$), other parameters were similar between the two groups (Table 4).

However, the mean VAS score showed no difference in mask tolerance between the two groups ($P = 0.25$). Similarly, the total time of noninvasive ventilation (NIV) was similar in the two groups ($P = 0.14$) as shown in Table 5. Intubation

Table 1: Age, gender, and comorbidities in patients in the two groups.

	TFM $N = 24$	ONM $N = 24$	P value
Age	63.21 ± 10.62	67.83 ± 9.46	0.118
Sex			
Male	13 (54.2%)	15 (62.5%)	0.558
Female	11 (45.8%)	9 (37.5%)	
Comorbidities			
ALS	1 (4.2%)	0 (0.0%)	
Bronchiectasis	2 (8.3%)	2 (8.3%)	
COPD	20 (83.3%)	20 (83.3%)	>0.999
ILD	0 (0%)	1 (4.2%)	
OSA	1 (4.2%)	1 (4.2%)	

ALS: Amyotrophic Lateral Sclerosis; COPD: chronic obstructive pulmonary disease; ILD: Interstitial Lung Diseases; OSA: obstructive sleep apnea.

Table 2: Comparison of clinical and oxygenation parameters at baseline (time zero) and six hours after initiation of treatment.

Efficacy	TFM $N = 24$	ONM $N = 24$	P value
	Clinical		
HR			
Time 0	91.12 ± 11.96	90.25 ± 11.87	>0.999†
Time 6 h	86.09 ± 6.47	86.13 ± 9.47	0.987
RR			
Time 0	21.50 ± 3.28	21.63 ± 1.86	0.175†
Time 6 h	19.30 ± 2.38	19.92 ± 1.93	0.045†
SPO2			
In room	84.17 ± 6.81	81.0 ± 6.65	0.063†
With O2	90.37 ± 4.55	92.33 ± 2.99	0.365†
Frequency of patients using accessory muscles			
Time 0	4 (16.7%)	10 (41.7%)	0.057
Time 6 h	1 (4.3%)	6 (25.0%)	0.055

† Mann–Whitney U test.

was needed in two patients in ONM group and one patient in TFM group. One death occurred in each group.

Although both groups had similar IPAPs, EPAP was significantly higher in patients receiving NPPV via ONM (5.04 ± 0.81 cm H_2O in TFM, 6.17 ± 1.74 in ONM) ($P = 0.01$, Table 6).

4. Discussion

The purpose of this study was to compare the efficacy and outcome of delivering NPPV to patients with acute respiratory failure using TFM or ONM. We hypothesized that TFM would be superior as it is reported to be more comfortable for patients. However, the mean VAS scores were similar in the two groups and different masks did not affect total NIV time, phobia, skin inflammation, or mortality rate.

Holanda et al. reported equal patient comfort with TFM and ONM, less air leak, nasal bridge pain, mouth and throat dry mucosa by TFM, and less claustrophobia with ONM [8]. Criner et al. also reported TFM to be superior to ONM with respect to air leak and patient comfort [6]. Chacur et al. reported better patient tolerance with TFM but, unlike our findings, they showed longer NIV time in TFM users [9]. Subsequently, a case series reported effective, safe, and acceptable experience in four patients, three having ALS (Amyotrophic Lateral Sclerosis) and nasal necrosis and one experiencing acute respiratory failure immediately after extubation [10]. Ozsancak et al. reported similar results to ours although they reported a higher success rate after three hours of NPPV with ONM versus TFM [11].

Concerning clinical and laboratory parameters, we found no obvious change or difference in heart rate or the use of accessory muscles after six hours of NIV, but respiratory rate was significantly lower in TFM users. This was consistent with the results of earlier studies, which showed no difference in heart rate, respiratory rate, or oxygen saturation after six hours of NPPV with TFM or ONM [8, 11]. On the contrary, Roy et al. reported significant reductions in heart rate and respiratory rate after one hour of NPPV via TFM in patients who had not tolerated other masks [7]. We compared VBG values (PCO_2, pH, HCO_3, and BE) at zero, one, six, and 24 hours after initiation of NPPV. We observed significant

Table 3: Paraclinical parameters at one, six, and 24 hours after initiation of treatment.

Efficacy	TFM $N = 24$	ONM $N = 24$	P value
	Para-clinical		
	PH		0.249††
0	7.31 ± 0.05	7.30 ± 0.07	0.885†
1 h	7.34 ± 0.06	7.33 ± 0.07	0.881†
6 h	7.34 ± 0.05	7.33 ± 0.06	0.598
24 h	7.36 ± 0.05	7.34 ± 0.04	0.266
	PCO2		0.840††
0	85.41 ± 15.24	87.17 ± 18.68	0.723
1 h	72.11 ± 16.67	79.33 ± 16.22	0.139
6 h	70.11 ± 13.61	77.97 ± 11.83	0.040
24 h	70.39 ± 11.59	52.93 ± 30.19	0.137†
	HCO3		0.392††
0	42.11 ± 5.52	42.44 ± 6.76	0.852
1 h	39.71 ± 5.89	41.48 ± 8.00	0.523†
6 h	37.55 ± 5.05	41.81 ± 6.41	0.015
24 h	39.86 ± 4.92	38.78 ± 6.75	0.541
	BE		0.906††
0	11.29 ± 4.64	11.34 ± 6.06	0.977
1 h	12.23 ± 10.63	11.29 ± 6.85	0.932†
6 h	8.71 ± 3.62	11.45 ± 6.03	0.067
24 h	10.67 ± 4.19	9.36 ± 5.95	0.392

† Mann–Whitney U test; †† repeated measures ANOVA.

Table 4: Comfort of the masks based on the items evaluated in the questionnaire.

Severity	TFM $N = 24$	ONM $N = 24$	P value
Pain			
Forehead	0.26 ± 0.54£	0.33 ± 0.70	0.941†
Nasal bridge	0.35 ± 0.49	0.67 ± 0.70	0.113†
Cheeks	0.04 ± 0.21	0.50 ± 0.78	0.011†
Chin	0.26 ± 0.62	0.12 ± 0.45	0.359†
Air leakage			
Eye area	0.74 ± 1.10	0.50 ± 0.66	0.683†
Mouth	0.17 ± 0.39	0.33 ± 0.64	0.455†
Dry mucosa			
Throat	0.74 ± 0.81	1.04 ± 0.99	0.309†
Nose	0.61 ± 0.89	0.50 ± 0.72	0.808†
Skin inflammation			
Itching	0.13 ± 0.62	0.21 ± 0.59	0.356†
Burning	0 ± 0	0 ± 0	>0.999†
Other			
Compression	0.48 ± 0.51	0.50 ± 0.59	>0.999†
Phobia	0.13 ± 0.34	0.04 ± 0.20	0.281†
Total questionnaire Score	3.91 ± 2.41	4.75 ± 3.03	0.323†

† Mann–Whitney U test; £: mean ± standard deviation of score given by patients in each group to the mask (from 0 to 3) based on the intensity of each complication experienced.

Table 5: Acceptance score, NPPV total time, intubation rate, and mortality rate in the two groups.

	TFM $N = 24$	ONM $N = 24$	P value
Mean VAS score	3.13 ± 0.92	3.37 ± 0.92	0.255†
NPPV total time	6.52 ± 3.24	8.71 ± 4.75	0.141†
Intubation	1 (4.2%)	2 (8.7%)	0.609
Death	1 (4.2%)	1 (4.2%)	>0.999

† Mann–Whitney U test.

Table 6: IPAP, EPAP, and O2 requirement within the first hour in the two groups.

Ventilator setting	TFM $N = 24$	ONM $N = 24$	P value
IPAP (cm H_2O)	13.21 ± 1.89	14.46 ± 3.13	0.273†
EPAP (cm H_2O)	5.04 ± 0.81	6.17 ± 1.74	0.010†
O2 (Lit/min)	8.13 ± 4.87	9.92 ± 3.43	0.180†

IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure.
† Mann–Whitney U test.

improvements in PCO_2 and HCO_3 after six hours in TFM group but the overall VBG alterations were the same in both groups. Criner et al. previously reported improved gas exchange in hypercapnic patients who received NPPV via TFM [6].

We also compared intubation rate and in-hospital mortality between the two groups, and similar to previous reports, we found no difference in either category [9, 11]. We also assessed patient comfort and found a lower score for pain in cheeks in patients receiving NPPV via TFM.

5. Conclusion

While TFM was more efficacious in reducing PCO2 and HCO3 during the first six hours of treatment, the blood gas alterations were the same in both groups based on repeated measures ANOVA once the patients were out of the acute phase of respiratory failure. Therefore, we may conclude that TFM was superior to ONM in acute phase of respiratory failure but not once the patients were out of acute phase. Our findings indicated that both TFM and ONM should be available in case of patient intolerance for one mask.

Additional Points

Study Limitations. Six patients opted out after randomization due to previous unpleasant experiences with NPPV.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

An earlier version of this work was presented as an abstract at 4th International Workshop on Lung Health Asthma and COPD, 2017.

References

[1] H. Kwok, J. McCormack, R. Cece, J. Houtchens, and N. S. Hill, "Controlled trial of oronasal versus nasal mask ventilation in the treatment of acute respiratory failure," *Critical Care Medicine*, vol. 31, no. 2, pp. 468–473, 2003.

[2] P. Navalesi, F. Fanfulla, P. Frigerio, C. Gregoretti, and S. Nava, "Physiologic evaluation of noninvasive mechanical ventilation delivered with three types of masks in patients with chronic hypercapnic respiratory failure," *Critical Care Medicine*, vol. 28, no. 6, pp. 1785–1790, 2000.

[3] A. M. Karnik, "Noninvasive positive pressure ventilation: testing the bridge," *Chest*, vol. 117, no. 3, pp. 625–627, 2000.

[4] M. Antonelli, G. Conti, M. Moro et al., "Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study," *Intensive Care Medicine*, vol. 27, no. 11, pp. 1718–1728, 2001.

[5] C. Girault, A. Briel, J. Benichou et al., "Interface strategy during noninvasive positive pressure ventilation for hypercapnic acute respiratory failure," *Critical Care Medicine*, vol. 37, no. 1, pp. 124–131, 2009.

[6] G. J. Criner, J. M. Travaline, K. J. Brennan, and D. T. Kreimer, "Efficacy of a new full face mask for noninvasive positive pressure ventilation," *Chest*, vol. 106, no. 4, pp. 1109–1115, 1994.

[7] B. Roy, F. C. Cordova, J. M. Travaline, G. E. D'Alonzo Jr., and G. J. Criner, "Full face mask for noninvasive positive-pressure ventilation in patients with acute respiratory failure," *Journal of the American Osteopathic Association*, vol. 107, no. 4, pp. 148–156, 2007.

[8] M. A. Holanda, R. C. Reis, G. F. P. Winkeler, S. C. B. Fortaleza, J. W. D. O. Lima, and E. D. B. Pereira, "Influence of total face, facial and nasal masks on short-term adverse effects during noninvasive ventilation," *Jornal Brasileiro de Pneumologia*, vol. 35, no. 2, pp. 164–173, 2009.

[9] F. H. Chacur, L. M. Vilella Felipe, C. G. Fernandes, and L. C. O. Lazzarini, "The total face mask is more comfortable than the oronasal mask in noninvasive ventilation but is not associated with improved outcome," *Respiration*, vol. 82, no. 5, pp. 426–430, 2011.

[10] I. Belchior, M. R. Gonçalves, and J. C. Winck, "Continuous noninvasive ventilation delivered by a novel total face mask: a case series report," *Respiratory Care*, vol. 57, no. 3, pp. 449–453, 2012.

[11] A. Ozsancak, S. S. Sidhom, T. N. Liesching, W. Howard, and N. S. Hill, "Evaluation of the total face mask for noninvasive ventilation to treat acute respiratory failure," *Chest*, vol. 139, no. 5, pp. 1034–1041, 2011.

Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 2834956, 7 pages
https://doi.org/10.1155/2017/2834956

Review Article

Harmful Effects of Hyperoxia in Postcardiac Arrest, Sepsis, Traumatic Brain Injury, or Stroke: The Importance of Individualized Oxygen Therapy in Critically Ill Patients

Jean-Louis Vincent,[1] Fabio Silvio Taccone,[1] and Xinrong He[2]

[1]*Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, 1070 Brussels, Belgium*
[2]*Department of Intensive Care, Sun Yat-sen University Cancer Center, Guangzhou 510060, China*

Correspondence should be addressed to Jean-Louis Vincent; jlvincent@intensive.org

Received 13 November 2016; Accepted 27 December 2016; Published 26 January 2017

Academic Editor: Wan-Jie Gu

The beneficial effects of oxygen are widely known, but the potentially harmful effects of high oxygenation concentrations in blood and tissues have been less widely discussed. Providing supplementary oxygen can increase oxygen delivery in hypoxaemic patients, thus supporting cell function and metabolism and limiting organ dysfunction, but, in patients who are not hypoxaemic, supplemental oxygen will increase oxygen concentrations into nonphysiological hyperoxaemic ranges and may be associated with harmful effects. Here, we discuss the potentially harmful effects of hyperoxaemia in various groups of critically ill patients, including postcardiac arrest, traumatic brain injury or stroke, and sepsis. In all these groups, there is evidence that hyperoxia can be harmful and that oxygen prescription should be individualized according to repeated assessment of ongoing oxygen requirements.

1. Introduction

Oxygen is the third most abundant element in the universe and essential for life, but it was only officially "discovered" in the early 1770s separately by the British-born theologian, Joseph Priestly, and the Swedish apothecary, Carl Scheele [1, 2]. It took another few years for its role in respiration to be identified by the French chemist, Antoine-Laurent Lavoisier, who also gave it its name [1, 2]. Introduced into anaesthetic practice in the 1930s, oxygen is now one of the most widely used "drugs" in hospitalized patients. In a point-prevalence study conducted in 40 intensive care units (ICUs) in Australia and New Zealand in 2012, 59% of patients were receiving mechanical ventilation; among those not receiving mechanical ventilation, 86% were receiving oxygen via nasal cannulas, facial masks, or noninvasive ventilation [3]. However, although oxygen therapy clearly has important benefits in many patients, we have become increasingly aware of the potential harmful effects of high oxygenation concentrations in blood and tissues (Figure 1). In a retrospective study comparing mortality rates and PaO_2 levels in mechanically ventilated ICU patients, de Jonge et al. reported a U-shaped relationship with increased mortality rates at low and high PaO_2 [4]. The potential risks of hyperoxia, with a focus on recent clinical evidence in specific groups of critically ill patients (Table 1), will be the emphasis of this short narrative review.

2. Effects of Hyperoxia

Adequate cellular oxygenation is essential for normal cell function, and a low SaO_2 is life-threatening, especially in acute conditions. Providing supplementary oxygen will increase oxygen delivery in hypoxaemic patients, thus supporting cell function and metabolism and limiting organ dysfunction. However, in patients who are not hypoxaemic, supplemental oxygen will increase oxygen concentrations into hyperoxaemic ranges. Although human beings may be exposed to hypoxia, for example, when at altitude or as a result of pulmonary disease, we are never exposed to hyperoxia,

Table 1: Some recent clinical studies on the risks of hyperoxia after cardiac arrest or myocardial infarction, in traumatic brain injury, stroke, sepsis, and mixed ICU patients.

References	Study design	Hyperoxia measurements	Main finding
After cardiac arrest or myocardial infarction			
Kilgannon et al. 2010 [11].	Retrospective cohort study, 120 hospitals, 6326 patients (nontraumatic cardiac arrest)	First PaO_2 in the first 24 hours. Hyperoxia: $PaO_2 \geq 300$ mmHg	Hyperoxia was associated with an increased hospital mortality compared with either hypoxia or normoxia (OR 1.8 [1.5–2.2])
Bellomo et al. 2011 [23]	Retrospective cohort study, 125 ICUs, 12108 patients (nontraumatic cardiac arrest)	Worst PaO_2 in first 24 h. Hyperoxia: $PaO_2 \geq 300$ mmHg Normoxia: PaO_2 60–300 mmHg	Hyperoxia group had a higher hospital mortality than normoxia (OR 1.2 [1.1–1.6])
Kilgannon et al. 2011 [24]	Retrospective cohort study, 120 hospitals, 4459 patients (nontraumatic cardiac arrest)	Highest PaO_2 in the first 24 hours	A 100 mmHg increase in PaO_2 was associated with a 24% increase in mortality risk (OR 1.24 [1.18 to 1.31])
Ranchord et al. 2012 [25]	Pilot randomized controlled trial, single-centre, 136 patients with STEMI	Patients randomized to receive high-concentration (6 L/min) or titrated oxygen (to achieve oxygen saturation 93%–96%) for 6 hours after presentation	No differences in number of deaths in the two groups (relative risk 0.5, 95% CI 0.05–5.4, $p = 0.56$)
Janz et al. 2012 [26]	Retrospective analysis of a prospective cohort study, single-centre 170 patients (cardiac arrest treated with mild therapeutic hypothermia)	Highest PaO_2 in first 24 h.	Increased hospital mortality for every 100 mmHg increase in PaO_2 (OR 1.49 [1.03, 2.14])
Lee et al. 2014 [27]	Retrospective cohort study, single-centre, 213 patients (cardiac arrest treated with therapeutic hypothermia)	Average PaO_2 between ROSC and the end of rewarming. Hyperoxia: $PaO_2 > 157$ mmHg Normoxia: PaO_2 117–135 mmHg	V-shaped association between PaO_2 and poor neurologic outcome at hospital discharge (OR 6.47 [1.68, 24.91])
Stub et al. 2015 [14]	Prospective, randomized, controlled trial, 9 hospitals, 441 patients with STEMI	Patients with an $SpO_2 > 94\%$ were randomized to receive 8 L/min of oxygen or no supplemental oxygen from arrival of paramedics until transfer to the cardiac care unit	An increased rate of recurrent myocardial infarction, an increase in the frequency of cardiac arrhythmias, and an increase in myocardial infarct size at 6 months on magnetic resonance imaging in the supplement group
Elmer et al. 2015 [12]	Retrospective analysis of a high-resolution database, single-centre, 184 patients postcardiac arrest	Mean hourly exposure in first 24 h. Normoxia: PaO_2 60–100 mmHg; Moderate hyperoxia: PaO_2 101–299 mmHg; Severe hyperoxia: $PaO_2 \geq 300$ mmHg	Severe hyperoxia was associated with decreased survival (OR 0.83 [0.69–0.99] per hour exposure); moderate hyperoxia was not associated with survival but with improved SOFA score 24 h (OR 0.92 [0.87–0.98])
Eastwood et al. 2016 [13]	Retrospective before-after nested cohort study, single-centre, 50 patients postcardiac arrest	Conservative oxygenation: SpO_2 88–92%	Conservative group had a shorter ICU length of stay; no difference in the proportion of survivors discharged from hospital with good neurological outcome compared to conventional group
In traumatic brain injury (TBI) and stroke			
Davis et al. 2009 [18]	Retrospective cohort study, 5 trauma centres, 3420 moderate-to-severe patients	Extreme hyperoxia: first $PaO_2 >$ 487 mmHg	A PaO_2 value of 110–487 mmHg was considered optimal. Extreme hyperoxia had an independent association with decreased survival (OR 0.50 [0.36, 0.71]) compared to optimal range
Brenner et al. 2012 [19]	Retrospective study, single-centre, 1547 severe TBI patients	Mean PaO_2 in first 24 h hospital admission: Hyperoxia: $PaO_2 > 200$ mmHg Normoxia: PaO_2 100–200 mmHg	Both low and high PaO_2 had increased mortality. Patients with hyperoxia had higher hospital mortality (OR 1.50 [1.15–1.97]) and lower discharge GCS scores at discharge (OR 1.52 [1.18–1.96])

Table 1: Continued.

References	Study design	Hyperoxia measurements	Main finding
Raj et al. 2013 [20]	Retrospective nested cohort analysis, 5 hospitals, 1116 ventilated moderate-to-severe TBI patients	Worst PaO_2 in first 24 h ICU admission: Hyperoxia: PaO_2 > 100 mmHg Normoxia: PaO_2 75–100 mmHg	Hyperoxia had no independent relationship with in-hospital mortality (OR 0.94 [0.65–1.36]) and 6-month mortality (OR 0.88 [0.63–1.22])
Rincon et al. 2014 [28]	Retrospective cohort, 84 ICUs, 2894 stroke patients	PaO_2 in the first 24 hours. Hyperoxia: $PaO_2 \geq 300$ mmHg Normoxia: PaO_2 60–300 mmHg	Hyperoxia was independently associated with in-hospital mortality (OR 1.22 [1.04–1.48])
Rincon et al. 2014 [29]	Retrospective cohort study, 61 hospitals, 1212 ventilated TBI patients	Hyperoxia: PaO_2 > 300 mmHg Normoxia: PaO_2 60–300 mmHg	Hyperoxia was associated with a higher in-hosptial case fatality (OR 1.5 [1.02–2.4])
Jeon et al. 2014 [30]	Prospective, observational cohort database analysis, single-centre, 252 patients (subarachnoid haemorrhage)	PaO_2 AUC by observation time until delayed cerebral ischemia (DCI). Hyperoxia: $PaO_2 \geq 173$ mmHg (upper quartile)	Hyperoxia group had a higher incidence of DCI (OR 3.16 [1.69 to 5.92]) and poor outcome (modified Rankin Scale 4–6 at 3 months after subarachnoid haemorrhage) (OR 2.30 [1.03 to 5.12])
Quintard et al. 2015 [17]	Retrospective analysis of a database, single-centre, 36 severe TBI patients	Hyperoxia: PaO_2 > 150 mmHg	Hyperoxia was associated with increased cerebral microdialysis glutamate, indicating cerebral excitotoxicity
Lang et al. 2016 [31]	Retrospective analysis using 2 databases, 432 ventilated patients (subarachnoid haemorrhage)	Time-weighted average PaO_2 during the first 24 hours Low PaO_2 < 97.5 mmHg; Intermediate PaO_2 97.5–150 mmHg; High PaO_2 >150 mmHg	Patients with an unfavorable outcome had significantly higher PaO_2, but high PaO_2 has no effect on 3-month neurological outcomes (OR 1.09 [0.61–1.97]) or mortality (OR 0.73 [0.38–1.40])
In sepsis			
Stolmeijer et al. 2014 [32]	Prospective pilot study, 83 sepsis patients in emergency department, single-centre	PaO_2 after 5 min of a VentiMask 40% with 10 L O_2/min. Hyperoxia: PaO_2 > 100 mmHg	Of the hyperoxic patients, 8% died in hospital versus 6% with normoxia
In mixed ICU patients			
de Jonge et al. 2008 [4]	Retrospective observational study, 50 ICUs, 36307 ventilated patients	Worst PaO_2 in first 24 h. Hyperoxia: $PaO_2 \geq 123$ mmHg (upper quintile) compared with PaO_2 between 67 and 80 mmHg	In-hospital mortality was linearly related to FiO_2 value and had a U-shaped relationship with PaO_2. Hyperoxia had a higher mortality (OR 1.23 [1.13–1.34])
Panwar et al. 2016 [33]	Pilot randomized controlled trial, 4 ICUs, 103 patients	Conservative oxygenation: SpO_2 88–92% Liberal oxygenation: $SpO_2 \geq 96\%$	No significant differences in measures of new organ dysfunction, or ICU or 90-day mortality (OR 0.77 [0.40–1.50])
Girardis et al. 2016 [34]	Open-label randomized trial, single-centre, 434 patients	Conservative oxygenation: PaO_2 70–100 mmHg (SpO_2 94–98%) Conventional oxygenation: PaO_2 > 150 mmHg (SpO_2 97–100%)	Patients in the conservative group had lower ICU mortality (RR 0.57 [0.37–0.9]) and fewer episodes of shock, liver failure, and bacteraemia
Helmerhorst et al. 2017 [35]	Observational cohort study, 3 ICUs, 14441 ventilated patients	First PaO_2 at ICU admission Mild hyperoxia: PaO_2 120–200 mmHg Severe hyperoxia: PaO_2 > 200 mmHg	Severe hyperoxia was associated with higher mortality rates and fewer ventilator-free days in comparison to both mild hyperoxia and normoxia Time spent in hyperoxia had a linear and positive relationship with hospital mortality

OR: odds ratio; SOFA: sequential organ failure assessment; ROSC: return of spontaneous circulation; DIC: delayed cerebral ischemia; AUC: area under the curve; STEMI: ST-segment elevated myocardial infarction.

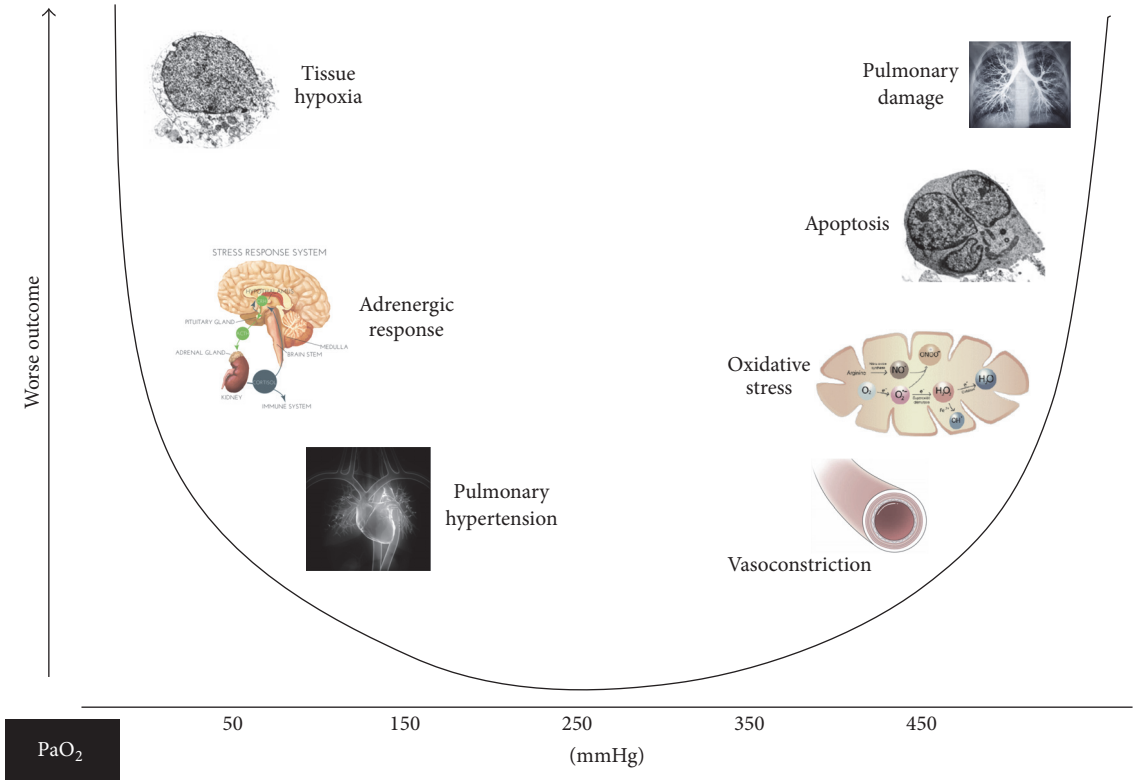


Figure 1: Schematic showing U-shaped association of PaO_2 with outcome.

so that supplying extra oxygen to individuals who are not hypoxaemic is always a "nonphysiological" event.

Hyperoxia is associated with multiple effects in different organ systems. It can directly damage tissues via the production of reactive oxygen species (ROS) in excess of physiological antioxidant defence capabilities [5], leading to increased cell death by apoptosis and increased release of endogenous damage-associated molecular pattern molecules (DAMPs) that stimulate an inflammatory response, notably in the lungs [6] and vasoconstriction, likely as a result of reduced nitric oxide levels [7]. Orbegozo Cortés et al. recently reported that normobaric hyperoxia in healthy volunteers was associated with reduced capillary perfusion as assessed using sublingual side-stream dark field (SDF) video-microscopy [8]. It has been suggested that these vasoconstrictive effects may provide a means of protecting cells from the harmful effects of high PaO_2 [9].

2.1. After Cardiac Arrest or Myocardial Infarction. Given the associated vasoconstriction and increased ROS release, hyperoxia may be particularly harmful after cardiac arrest [10]. Experimental and observational data have given conflicting results regarding the effects of hyperoxia in this setting [10]. In a retrospective analysis of data from 6326 post-cardiac arrest patients admitted to ICUs in 120 US hospitals between 2001 and 2005, patients with hyperoxia (defined as PaO_2 of ≥300 mmHg) on arrival in the ICU had higher mortality rates than those with normoxia or hypoxia; in multivariable analysis, hyperoxia exposure was an independent predictor of in-hospital death (odds ratio 1.8 [95% CI 1.5–2.2], $p < 0.001$) [11]. In an analysis of a registry database, severe hyperoxia (as identified by a PaO_2 > 300 mmHg) was associated with increased mortality in post-cardiac arrest patients, whereas moderate or "probable" hyperoxia (PaO_2 101–299 mmHg) was not [12]. In a retrospective cohort study, patients managed according to a conservative oxygen approach after cardiac arrest, targeting an pulse oximetry oxygen saturation (SpO_2) of 88–92% had shorter lengths of ICU stay, although there were no differences in neurological outcomes [13]. In a multicentre trial conducted in 441 patients with ST-elevation myocardial infarction, patients with an SpO_2 > 94% were randomized to receive 8 L/min of oxygen or no supplemental oxygen from arrival of paramedics until transfer to the cardiac care unit. Patients treated with oxygen had an increased rate of recurrent myocardial infarction, an increase in the frequency of cardiac arrhythmias, and an increase in myocardial infarct size at 6 months on magnetic resonance imaging [14]. These results do not support the use of routine supplemental oxygen after cardiac arrest or myocardial infarction. A randomized multicentre study is ongoing in Sweden aiming to randomize 6,600 patients with suspected acute myocardial infarction and SpO_2 ≥ 90% to either 6 L/min of supplemental oxygen for 6 to 12 hours or room air [15].

2.2. In Traumatic Brain Injury and Stroke. Reduced cerebral oxygenation after brain injury is associated with impaired mitochondrial function and reduced metabolic rate and may

be associated with an increased risk of secondary brain damage [16, 17]. Treating such patients with hyperoxia may, therefore, be expected to have beneficial effects on outcomes. However, clinical studies have given conflicting results. In a retrospective study of more than 3000 patients with traumatic brain injury (TBI), hypoxaemia, and extreme hyperoxaemia (PaO_2 > 487 mmHg) on admission were both associated with worse outcomes; a PaO_2 value of 110–487 mmHg was considered optimal in this study [18]. Similar findings were reported by a more recent retrospective study in 1547 patients with TBI, with both low and high admission PaO_2 levels independently associated with worse outcomes [19]. In a long-term outcomes study after TBI, although there was a significant association between hyperoxaemia and a decreased risk of 6-month mortality in univariate analysis, in multivariable analysis, hyperoxaemia was not independently associated with outcome [20]. In a small randomized trial, 68 patients with severe TBI received either 80% or 50% oxygen via mechanical ventilation in the first 6 hours after the TBI. Patients in the hyperoxia group had better outcomes at 6 months as assessed using the Glasgow Outcome Scale than patients in the normoxia group [21]. A planned larger study to compare treatment with an FiO_2 of 0.4 or 0.7 in patients with TBI was terminated because of slow recruitment (NCT01201291). Interestingly, in a prospective study of 30 patients monitored with a brain tissue oxygen sensor, Vilalta et al. reported that a hyperoxia challenge was associated with improved cerebral metabolism only in patients with reduced metabolism at baseline [22].

Evidence from studies in patients with stroke is also conflicting. Lang et al. reported no effect on 3-month neurological outcomes or mortality of moderate hyperoxaemia during the first 24 hours after ICU admission in patients after subarachnoid haemorrhage [31], and Young et al. similarly reported no association between worst PaO_2 in the first 24 hours after ICU admission and mortality in patients with acute ischaemic stroke [36]. However, other observational studies have reported detrimental effects on short and longer term outcomes in different groups of stroke patients [28, 30]. A study randomizing patients to room air or supplemental oxygen administered at 30–45 L/min for 8 hours was terminated early because of more deaths in the oxygen group (NCT00414726). In a pilot study comparing oxygen supplementation for 72 h via nasal cannulae with room air in 289 patients with acute stroke, there was a small improvement in neurological recovery at one week [37], but there were no significant differences between the groups at 6 months [38], findings supported by the larger Stroke Oxygen Study in more than 8000 patients [39].

2.3. In Sepsis and Septic Shock. The use of hyperoxia in patients with sepsis is also controversial [40]. Sepsis is already associated with increased formation of ROS, believed to play a role in the tissue damage and organ dysfunction seen during sepsis. Hyperoxaemia is known to stimulate release of ROS and could therefore further worsen organ function in these patients. In a rat caecal ligation and puncture model, hyperoxia was associated with increased inflammatory cytokine release and organ dysfunction compared to normoxia [41]. However, in other animal models of sepsis, hyperoxia has been associated with improved haemodynamics and anti-inflammatory effects [42, 43]. And in a sheep model of sepsis, we showed that hyperoxia was associated with better haemodynamics and organ function compared to normoxia (unpublished data). In experimental human endotoxaemia, hyperoxia had no effect on levels of inflammatory mediators [44], and in a small observational study of patients with suspected sepsis in the emergency department, there were no significant differences in mortality rates between hyperoxic and normoxic patients [32]. A clinical trial in patients with sepsis randomized to hyperoxia or normoxia and hypertonic or isotonic saline in a 2×2 factorial design was stopped prematurely because of increased mortality rates in the hyperoxia and hypertonic saline arms (NCT01722422). Two randomized studies, one comparing supplemental oxygen titrated to different PaO_2 targets (105–135 mmHg versus 60–90 mmHg, O_2-ICU study, NCT02321072) and one comparing supplemental oxygen at 15 L/min to no supplemental oxygen (NCT02378545), are currently ongoing and should provide final answers as to whether or not patients with sepsis may benefit from hyperoxia.

2.4. In Mixed ICU Patients. Use of liberal oxygen therapy is frequent in critically ill patients [45] and severe hyperoxaemia (PaO_2 > 200 mmHg) is associated with higher mortality rates [35]. Interestingly, in three ICUs in the Netherlands, more than 70% of ICU patients had PaO_2 levels that were higher than the upper limits identified by the ICU clinicians treating them [46]. Several studies have now compared so-called conservative oxygen strategies targeting lower PaO_2 or SpO_2 values with conventional oxygen administration. Panwar et al. compared target SpO_2 values of 88–92% and ≥96% in 103 ICU patients and reported no significant differences between the groups in terms of organ function or ICU and 90-day mortality [33]. In the Oxygen-ICU study, which was terminated early, 434 patients were randomized to receive supplemental oxygen to maintain PaO_2 at 70–100 mmHg (SpO_2 94–98%) or to be managed conventionally allowing PaO_2 to reach 150 mmHg (SpO_2 97–100%) [34]. Patients in the conservative group had lower ICU mortality than those in the conventional group (relative risk 0.57 [95% CI 0.37–0.9]; $p = 0.01$).

3. Conclusions

For many years, the known risks of hypoxia and less known adverse effects of hyperoxia have led to many patients receiving liberal oxygenation to avoid hypoxaemia at all costs. Although good quality data remain limited, results from the latest clinical studies seem to suggest that hyperoxaemia may be associated with worse outcomes in some critically ill patients (Table 1). The trend is therefore moving towards a more conservative approach to oxygenation aimed at maintaining SpO_2 targets at 95–97%, although the optimal PaO_2 level has not yet been defined and will likely change during the course of a patient's illness. Indeed, there may be a time window during which patients may benefit from higher oxygen levels [47]. Further well-designed randomized

controlled trials in carefully selected groups of patients may help provide some definitive answers to these questions. As with other areas of intensive care management, oxygen therapy should be individualized. Patients who are hypoxaemic clearly need to receive supplemental oxygen, but ongoing requirements need to be reassessed on a regular basis to limit any risks associated with hyperoxia.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

References

[1] J. E. Heffner, "The story of oxygen," *Respiratory Care*, vol. 58, no. 1, pp. 18–31, 2013.

[2] J. W. Severinghaus, "Priestley, the furious free thinker of the enlightenment, and Scheele, the taciturn apothecary of Uppsala," *Acta Anaesthesiologica Scandinavica*, vol. 46, no. 1, pp. 2–9, 2002.

[3] R. L. Parke, G. M. Eastwood, and S. P. McGuinness, "Oxygen therapy in non-intubated adult intensive care patients: a point prevalence study," *Critical Care and Resuscitation*, vol. 15, no. 4, pp. 287–293, 2013.

[4] E. de Jonge, L. Peelen, P. J. Keijzers et al., "Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients," *Critical Care*, vol. 12, no. 6, article R156, 2008.

[5] C. Brueckl, S. Kaestle, A. Kerem et al., "Hyperoxia-induced reactive oxygen species formation in pulmonary capillary endothelial cells in situ," *American Journal of Respiratory Cell and Molecular Biology*, vol. 34, no. 4, pp. 453–463, 2006.

[6] T. E. Zaher, E. J. Miller, D. M. P. Morrow, M. Javdan, and L. L. Mantell, "Hyperoxia-induced signal transduction pathways in pulmonary epithelial cells," *Free Radical Biology and Medicine*, vol. 42, no. 7, pp. 897–908, 2007.

[7] F. Sjöberg and M. Singer, "The medical use of oxygen: a time for critical reappraisal," *Journal of Internal Medicine*, vol. 274, no. 6, pp. 505–528, 2013.

[8] D. Orbegozo Cortés, F. Puflea, K. Donadello et al., "Normobaric hyperoxia alters the microcirculation in healthy volunteers," *Microvascular Research*, vol. 98, pp. 23–28, 2015.

[9] E. Calzia, P. Asfar, B. Hauser et al., "Hyperoxia may be beneficial," *Critical Care Medicine*, vol. 38, no. 10, pp. S559–S568, 2010.

[10] A. M. Dell'Anna, I. Lamanna, J.-L. Vincent, and F. S. Taccone, "How much oxygen in adult cardiac arrest?" *Critical Care*, vol. 18, no. 5, article 555, 2014.

[11] J. H. Kilgannon, A. E. Jones, N. I. Shapiro et al., "Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality," *JAMA—Journal of the American Medical Association*, vol. 303, no. 21, pp. 2165–2171, 2010.

[12] J. Elmer, M. Scutella, R. Pullalarevu et al., "The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database," *Intensive Care Medicine*, vol. 41, no. 1, pp. 49–57, 2015.

[13] G. M. Eastwood, A. Tanaka, E. D. V. Espinoza et al., "Conservative oxygen therapy in mechanically ventilated patients following cardiac arrest: a retrospective nested cohort study," *Resuscitation*, vol. 101, pp. 108–114, 2016.

[14] D. Stub, K. Smith, S. Bernard et al., "Air versus oxygen in ST-segment-elevation myocardial infarction," *Circulation*, vol. 131, no. 24, pp. 2143–2150, 2015.

[15] R. Hofmann, S. K. James, L. Svensson et al., "DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial," *American Heart Journal*, vol. 167, no. 3, pp. 322–328, 2014.

[16] F. Xu, P. Liu, J. M. Pascual, G. Xiao, and H. Lu, "Effect of hypoxia and hyperoxia on cerebral blood flow, blood oxygenation, and oxidative metabolism," *Journal of Cerebral Blood Flow and Metabolism*, vol. 32, no. 10, pp. 1909–1918, 2012.

[17] H. Quintard, C. Patet, T. Suys, P. Marques-Vidal, and M. Oddo, "Normobaric hyperoxia is associated with increased cerebral excitotoxicity after severe traumatic brain injury," *Neurocritical Care*, vol. 22, no. 2, pp. 243–250, 2015.

[18] D. P. Davis, W. Meade Jr., M. J. Sise et al., "Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury," *Journal of Neurotrauma*, vol. 26, no. 12, pp. 2217–2223, 2009.

[19] M. Brenner, D. Stein, P. Hu, J. Kufera, M. Wooford, and T. Scalea, "Association between early hyperoxia and worse outcomes after traumatic brain injury," *Archives of Surgery*, vol. 147, no. 11, pp. 1042–1046, 2012.

[20] R. Raj, S. Bendel, M. Reinikainen et al., "Hyperoxemia and long-term outcome after traumatic brain injury," *Critical Care*, vol. 17, no. 4, article no. R177, 2013.

[21] A. Taher, Z. Pilehvari, J. Poorolajal, and M. Aghajanloo, "Effects of normobaric hyperoxia in traumatic brain injury: a randomized controlled clinical trial," *Trauma Monthly*, vol. 21, no. 1, Article ID e26772, 2016.

[22] A. Vilalta, J. Sahuquillo, M.-A. Merino et al., "Normobaric hyperoxia in traumatic brain injury: does brain metabolic state influence the response to hyperoxic challenge?" *Journal of Neurotrauma*, vol. 28, no. 7, pp. 1139–1148, 2011.

[23] R. Bellomo, M. Bailey, G. M. Eastwood et al., "Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest," *Critical Care*, vol. 15, no. 2, article no. R90, 2011.

[24] J. H. Kilgannon, A. E. Jones, J. E. Parrillo et al., "Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest," *Circulation*, vol. 123, no. 23, pp. 2717–2722, 2011.

[25] A. M. Ranchord, R. Argyle, R. Beynon et al., "High-concentration versus titrated oxygen therapy in ST-elevation myocardial infarction: a pilot randomized controlled trial," *American Heart Journal*, vol. 163, no. 2, pp. 168–175, 2012.

[26] D. R. Janz, R. D. Hollenbeck, J. S. Pollock, J. A. McPherson, and T. W. Rice, "Hyperoxia is associated with increased mortality in patients treated with mild therapeutic hypothermia after sudden cardiac arrest," *Critical Care Medicine*, vol. 40, no. 12, pp. 3135–3139, 2012.

[27] B. K. Lee, K. W. Jeung, H. Y. Lee et al., "Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia," *American Journal of Emergency Medicine*, vol. 32, no. 1, pp. 55–60, 2014.

[28] F. Rincon, J. Kang, M. Maltenfort et al., "Association between hyperoxia and mortality after stroke: a multicenter cohort study," *Critical Care Medicine*, vol. 42, no. 2, pp. 387–396, 2014.

[29] F. Rincon, J. Kang, M. Vibbert, J. Urtecho, M. K. Athar, and J. Jallo, "Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicentre cohort study," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 85, no. 7, pp. 799–805, 2014.

[30] S.-B. Jeon, H. A. Choi, N. Badjatia et al., "Hyperoxia may be related to delayed cerebral ischemia and poor outcome after subarachnoid haemorrhage," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 85, pp. 1301–1307, 2014.

[31] M. Lang, R. Raj, M. B. Skrifvars et al., "Early moderate hyperoxemia does not predict outcome after aneurysmal subarachnoid hemorrhage," *Neurosurgery*, vol. 78, no. 4, pp. 540–545, 2016.

[32] R. Stolmeijer, J. C. Ter Maaten, J. G. Zijlstra, and J. J. M. Ligtenberg, "Oxygen therapy for sepsis patients in the emergency department: a little less?" *European Journal of Emergency Medicine*, vol. 21, no. 3, pp. 233–235, 2014.

[33] R. Panwar, M. Hardie, R. Bellomo et al., "Conservative versus liberal oxygenation targets for mechanically ventilated patients. A pilot multicenter randomized controlled trial," *American Journal of Respiratory and Critical Care Medicine*, vol. 193, no. 1, pp. 43–51, 2016.

[34] M. Girardis, S. Busani, E. Damiani et al., "Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU randomized clinical trial," *The Journal of the American Medical Association*, vol. 316, no. 15, pp. 1583–1589, 2016.

[35] H. J. Helmerhorst, D. L. Arts, M. J. Schultz et al., "Metrics of arterial hyperoxia and associated outcomes in critical care," *Critical Care Medicine*, vol. 45, no. 2, pp. 187–195, 2017.

[36] P. Young, R. Beasley, M. Bailey et al., "The association between early arterial oxygenation and mortality in ventilated patients with acute ischaemic stroke," *Critical Care and Resuscitation*, vol. 14, no. 1, pp. 14–19, 2012.

[37] C. Roffe, K. Ali, A. Warusevitane et al., "The SOS pilot study: a RCT of routine oxygen supplementation early after acute stroke—effect on recovery of neurological function at one week," *PLoS ONE*, vol. 6, no. 5, Article ID e19113, 2011.

[38] K. Ali, A. Warusevitane, F. Lally et al., "The stroke oxygen pilot study: a randomized controlled trial of the effects of routine oxygen supplementation early after acute stroke—effect on key outcomes at six months," *PLoS ONE*, vol. 8, no. 6, Article ID e59274, 2013.

[39] S. Hafner, F. Beloncle, A. Koch, P. Radermacher, and P. Asfar, "Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update," *Annals of Intensive Care*, vol. 5, no. 1, article 42, pp. 1–14, 2015.

[40] P. Asfar, E. Calzia, M. Huber-Lang, A. Ignatius, and P. Radermacher, "Hyperoxia during septic Shock—Dr. Jekyll or Mr. Hyde?" *Shock*, vol. 37, no. 1, pp. 122–123, 2012.

[41] R. Rodríguez-González, J. L. Martín-Barrasa, Á. Ramos-Nuez et al., "Multiple system organ response induced by Hyperoxia in a clinically relevant animal model of sepsis," *Shock*, vol. 42, no. 2, pp. 148–153, 2014.

[42] B. Hauser, E. Barth, G. Bassi et al., "Hemodynamic, metabolic, and organ function effects of pure oxygen ventilation during established fecal peritonitis-induced septic shock," *Critical Care Medicine*, vol. 37, no. 8, pp. 2465–2469, 2009.

[43] D. Waisman, V. Brod, M. A. Rahat et al., "Dose-related effects of hyperoxia on the lung inflammatory response in septic rats," *Shock*, vol. 37, no. 1, pp. 95–102, 2012.

[44] D. Kiers, J. Gerretsen, E. Janssen et al., "Short-term hyperoxia does not exert immunologic effects during experimental murine and human endotoxemia," *Scientific Reports*, vol. 5, article 17441, 2015.

[45] S. Suzuki, G. M. Eastwood, L. Peck, N. J. Glassford, and R. Bellomo, "Current oxygen management in mechanically ventilated patients: a prospective observational cohort study," *Journal of Critical Care*, vol. 28, no. 5, pp. 647–654, 2013.

[46] H. J. Helmerhorst, M. J. Schultz, P. H. van der Voort et al., "Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses," *Annals of Intensive Care*, vol. 4, article 23, 2014.

[47] N. Ridler, J. Plumb, and M. Grocott, "Oxygen therapy in critical illness: friend or foe? A review of oxygen therapy in selected acute illnesses," *Journal of the Intensive Care Society*, vol. 15, no. 3, pp. 190–198, 2014.

Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 3782401, 6 pages
https://doi.org/10.1155/2017/3782401

Clinical Study

The Effect of the Treatment with Heated Humidified High-Flow Nasal Cannula on Neonatal Respiratory Distress Syndrome in China: A Single-Center Experience

Ge Zheng,[1,2] Xiao-qiu Huang,[2] Hui-hui Zhao,[2] Guo-Xing Jin,[2] and Bin Wang[3]

[1]*Southern Medical University, Guangzhou, Guangdong Province, China*
[2]*Department of Paediatrics, Ruian People's Hospital, Wenzhou, Zhejiang, China*
[3]*Department of Paediatrics, Zhujiang Hospital of Southern Medical University, Guangzhou, Guangdong Province, China*

Correspondence should be addressed to Bin Wang; 402652217@qq.com

Received 20 October 2016; Revised 28 November 2016; Accepted 14 December 2016; Published 12 January 2017

Academic Editor: Zhongheng Zhang

Background. Noninvasive respiratory support is considered the optimal method of providing assistance to preterm babies with breathing problems, including nasal continuous positive airway pressure (NCPAP) and humidified high flow nasal cannula (HHHFNC). The evidence of the efficacy and safety of HHHFNC used as the primary respiratory support for respiratory distress syndrome (RDS) is insufficient in low- and middle-income countries. *Objective*. To investigate the effect of heated humidified high flow nasal cannula on neonatal respiratory distress syndrome compared with nasal continuous positive airway pressure. *Methods*. An observational cross-sectional study was performed at a tertiary neonatal intensive care unit in suburban Wenzhou, China, in the period between January 2014 and December 2015. *Results*. A total of 128 infants were enrolled in the study: 65 in the HHHFNC group and 63 in the NCPAP group. The respiratory support with HHHFNC was similar to that with NCPAP with regard to the primary outcome. There is no significant difference between two groups in secondary outcomes. Comparing with NCPAP group, the incidence of nasal damage was lower in HHHFNC group. *Conclusions*. HHHFNC is an effective and well-tolerated strategy as the primary treatment of mild to moderate RDS in preterm infants older than 28 weeks of GA.

1. Introduction

Neonatal respiratory distress syndrome (RDS) is one of the most common morbidities in preterm infants and may be treated with noninvasive respiratory support such as nasal continuous positive airway pressure (NCPAP) [1]. However, the use of NCPAP may lead to different degrees of damage to the nose, such as nasal swelling, nasal septum necrosis, and other complications, some even requiring surgery [2].

Humidified high-flow nasal cannula (HHFNC) is getting popular as a modality of noninvasive respiratory support for preterm infants [3]. Some evidence from early studies confirms that the use of HHHFNC may be linked with reduced work of breathing, benefited from ventilation, and reduced the demand for intubation in infants with respiratory distress syndrome [4]. Despite its increasing popularity, only a few large randomized clinical trials (RCTs) have been carried out to assess the efficacy and safety of HHHFNC in newborn infants in the world. Most of the RCT were performed after extubation and in larger infants [5]. Thus, there is a need for more data on primary therapy for RDS, especially in middle-income countries. It can hardly be denied that China's medical resources and number of healthcare professionals are still insufficient and HHHFNC might be of great importance in middle-income countries. The objective of our study is to investigate the effect of heated humidified high-flow nasal cannula on neonatal respiratory distress syndrome (RDS) compared with nasal continuous positive airway pressure as the primary noninvasive respiratory support.

2. Methods

This is an observational cross-sectional study performed on 128 preterm infants who are categorized into two groups; the

first group received NCPAP and the second group received HHHFNC. This study was performed in a level III neonatal intensive care unit (NICU) in suburban Wenzhou, Zhejiang Province, China, in the period between January 2014 and December 2015.

Infants were eligible for the study if they matched the following inclusion criteria: (1) GA of 28 weeks 0 days (28^{+0} weeks) to 34 weeks 6 days (34^{+6} weeks) and birth weight >1000 g; (2) mild to moderate RDS requiring noninvasive respiratory support, characterized by a fraction of inspired oxygen (FiO_2) lower than 0.3 for target saturation of peripheral oxygen (SpO_2) 88% to 93%; (3) parental consent obtained. Patients were ineligible if they presented with the following: (1) signs of serious, life-threatening malformations; (2) severe RDS requiring early intubation according to the American Academy of Paediatrics guidelines for neonatal resuscitation [6]; (3) severe intraventricular hemorrhage.

Provision of controlled early neonatal respiratory distress syndrome (CPAP) (T-piece) is now the main way of providing safe stabilization of preterm babies immediately after birth in our hospital. Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies >26 weeks when FiO_2 requirements >0.40 [7]. Infants who met prespecified criteria received surfactant via an INSURE (Intubation, Surfactant Administration, Extubation) technique. We enrolled preterm infants at the time of application of NCPAP or HHHFNC. The decision of putting the baby on NCPAP or HHHFNC was according to the attending neonatologist's decision; both modalities are used in our NICU for neonates requiring respiratory support.

The study was approved by the local medical research ethics committee and written informed consent of parents was obtained. HHHFNC was delivered by the Optiflow Junior (Fisher & Paykel Healthcare, New Zealand) or Vapotherm (Vapotherm, Exeter, USA). Nasal CPAP support was provided by the Arabella (Hamilton Medical, Inc., Bonaduz, Switzerland) utilizing pressures ranging from 3 to 8 cm H_2O.

Infants assigned to the HHHFNC group received an initial gas flow of 6 to 8 liters per minute. The size of the nasal cannula was determined according to the manufacturers' instructions in order to maintain a leak at the nares. The maximum permissible gas flow was 8 liters per minute, as recommended by the manufacturer. In the infants assigned to NCPAP, the starting pressure was 4 to 6 cm of water, achieved with a ventilator. Treatment was delivered through short binasal prongs, with sizing determined according to the manufacturer's recommendations. The maximum permissible pressure was 8 cm of water. Changes in respiratory support were made in steps of 1 liter per minute (for high-flow therapy) or 1 cm of water (for NCPAP). All infants were evaluated at least once a day.

Weaning from noninvasive respiratory support was considered if there was clinical improvement and the infants were receiving a fraction of inspired oxygen of 0.3 or lower, whereas discontinuation of noninvasive support was considered in infants who were receiving a fraction of inspired oxygen of 0.3 or lower, with gas flow of 4 liters per minute (in the HHHFNC group) or pressure of 5 cm of water (in the NCPAP group); earlier cessation of support could be ordered at the discretion of the treating clinician.

The primary outcome is intervention failure within 7 days after noninvasive respiratory support defined as requiring endotracheal intubation and mechanical ventilation. Secondary outcomes include the incidence of bronchopulmonary dysplasia (BPD) (requirement for supplemental oxygen and/or respiratory support at 36 weeks' postmenstrual age (PMA) for infants born at less than 32 weeks' gestational age or at 28 days of age for infants born at 32 weeks' gestational age or later), pneumothorax, severe intraventricular hemorrhage (IVH, Papile's grade 3 or 4), retinopathy of prematurity (ROP), nasal trauma, time until full feeds (when full enteral feeding was achieved ≥120 mL/kg per day), late-onset sepsis, necrotizing enterocolitis (NEC), and length of stay.

The criteria for intubation were the following: (1) apnea despite 30 seconds of positive pressure ventilation; (2) FiO_2 greater than 0.6 to maintain SpO_2 more than 88%; (3) persistent marked/severe retractions; (4) cardiovascular collapse (heart rate less than 60 beats per minute or shock); (5) severe metabolic acidosis (arterial base deficit less than −10); (6) severe respiratory acidosis (arterial PCO_2 more than 65 mmHg).

3. Statistical Analysis

The data are normally distributed continuous variables expressed as mean ± standard deviation, skewness distribution by median (interquartile range) representation. Normally distributed continuous variables between groups were compared using Student's t-test, skewed distribution by test using Wilcoxon Mann–Whitney U test. Dichotomous outcomes were compared by χ^2 test or Fisher's exact test. Two-sided P values 0.05 were considered statistically significant, and no adjustments were made for multiple comparisons. All analyses were performed with the use of SPSS (version 19; IBM, Armonk, NY).

4. Results

A total of 128 infants were involved in the study between January 2014 and December 2015, 65 in the HHHFNC group and 63 in the NCPAP group. The baseline characteristics of the two groups were similar at the time of treatment (Table 1). The group of HHHFNC was similar to the NCPAP group with regard to the primary outcome (Table 2). Regarding the failure from the start of the study within 7 days of noninvasive respiratory support, in the group of HHHFNC of 65 patients, 13 cases failed (20%), while in the NCPAP group of 63 infants, 11 cases (17.5%) failed (95% CI of risk difference, 0.5% to 2.9%; $P = 0.71$) (Table 2). There was no significant difference in failure rates between the 2 groups at any of the gestational age (Table 2).

There were no significant differences between the 2 groups in most of the secondary respiratory outcomes except for nasal trauma rates (Tables 3 and 4). The HHHFNC and NCPAP groups were similar in overall duration of respiratory

Table 1: Demographic characteristics of the study population.

Characteristic	HHHFNC ($n = 65$)	NCPAP ($n = 63$)
Gestational age, week, mean (SD)	31.9 (1.7)	31.9 (1.8)
<32 weeks, *n* (%)	20 (30.8)	22 (34.9)
Birth weight, mean ± SD, g	1754 (299)	1790 (373)
<1500 g, *n* (%)	16 (24.6)	16 (25.4)
Small for gestational age, number (%)	3 (4.6)	4 (6.3)
Female, number (%)	35 (53.8)	30 (47.6)
Multiple birth, number (%)	14 (21.5)	16 (25.4)
Antenatal steroids, number (%)	26 (40)	23 (36.5)
Cesarean delivery, number (%)	35 (53.8)	31 (49.2)
Neonatal resuscitation, number (%)	38 (58.5)	35 (55.6)
Apgar score at 5 min, median (IQR)	9 (8-9)	9 (8-9)
Prestudy surfactant, *n* (%)	20 (30.8)	22 (34.9)
Prestudy caffeine, *n* (%)	24 (36.9)	25 (39.7)
pH before enrollment, mean (SD)	7.19 (0.06)	7.19 (0.06)
PCO_2 before enrollment, mean (SD), mmHg	55.3 (3.3)	55.5 (3.5)
FIO_2 before enrollment, median (IQR)	0.23 (0.21–0.30)	0.25 (0.21–0.30)

FIO_2, fraction of inspired oxygen; HHHFNC, heated, humidified high-flow nasal cannula; IQR, interquartile range; NCPAP, nasal continuous positive airway pressure; PCO_2, partial pressure of carbon dioxide.
$P > 0.05$ for all comparisons.

Table 2: Primary outcome results.

Outcome	HHHFNC ($n = 65$)	NCPAP ($n = 63$)	95% CI of risk difference	*P* value[a]
Mechanical ventilation within 7 days, number (%)	13 (20)	11 (17.5)	0.5 to 2.9	0.71
Gestational age[b]				
28^{+0} to 32^{+6}	9 (23.7)	8 (21.1)	0.4 to 3.4	0.78
33^{+0} to 34^{+6}	4 (14.8)	3 (12)	0.3 to 6.4	0.77
Age at the start of mechanical ventilation, median (IQR), h	35.2 (6–90)	22.3 (4–80)	−8.35 to 34.12	0.21
Duration of mechanical ventilation, median (IQR), d	3.3 (1 to 5)	3.5 (2 to 5)	−1.32 to 0.84	0.87

HHHFNC, heated, humidified high-flow nasal cannula; IQR, interquartile range; NCPAP, nasal continuous positive airway pressure. [a]Dichotomous outcomes were compared by χ^2 test; continuous outcomes were compared by Wilcoxon 2-sample test. [b]Gestational age is presented as weeks$^{+\text{days}}$.

support (median [IQR], 5.6 [3.0 to 15.0] versus 5.1 [2.0 to 14.0] days; 95% CI of difference in medians, −0.32 to 1.33; $P = 0.72$), days of noninvasive respiratory support (median [IQR], 5.2 [3.0 to 13.0] versus 4.8 [2.0 to 13.0] days; 95% CI of difference in medians, −0.25 to 1.06; $P = 0.31$), days of oxygen supplementation (median [IQR], 0.4 [0.0 to 3.0] versus 0.3 [0.0 to 3.0]; 95% CI of difference in medians, −0.19 to 0.38; $P = 0.26$), need for surfactant (38.5% versus 42.9%; 95% CI of risk difference, 0.41 to 1.69; $P = 0.61$), duration of caffeine treatment (median [IQR], 3.2 [0.0 to 24.0] versus 2.0 [0.0 to 22.0] days; 95% CI of difference in medians, −0.23 to 2.51; $P = 0.68$), and the rate of air leaks (3.1% versus 1.6%; 95% CI of risk difference, 0.17 to 22.3; $P = 0.58$). Finally, we found no significant difference between the two groups in the rate of BPD (9.2% versus 9.5%; 95% CI of risk difference, 0.29 to 3.2; $P = 0.96$) (Table 3). Any acute adverse events besides air leaks and long-term complications of prematurity were strictly monitored after study entry. The 2 groups did not show significant difference for any of them (Table 3). The total number of deaths is two: 1 case in the HHHFNC group (28 weeks, died at 40 days with septic shock) and the other case in the NCPAP group (29 weeks at 16 days with NEC). The overall rate of sepsis was similar between the 2 groups. The combined outcome of "any adverse event" was not significantly different between the 2 groups. The rate of nasal trauma was significantly lower in the HHHFNC group than that in the NCPAP group (21.5% versus 42.9%; 95% CI of risk difference, 0.17 to 0.79; $P = 0.01$) (Table 4). Finally, no statistically significant differences were found in duration of hospitalization, full enteral feeding, weight, or exclusive breastfeeding at discharge (Table 4).

5. Discussion

In this study, we did not find significant differences in neonates older than 28 weeks of gestational age receiving noninvasive respiratory support with HHHFNC or NCPAP in the primary outcome: treatment failure within the first 7 days. In addition, we found no difference between two groups in respiratory support results, including oxygen supplementation time, diagnosing BPD, or hospital discharge for

Table 3: Respiratory support outcomes among infants assigned to HHHFNC compared with NCPAP.

Outcome	HHHFNC ($n = 65$)	NCPAP ($n = 63$)	95% CI of risk difference	P value
Duration received, median (IQR), d				
Respiratory support	5.6 (3 to 15)	5.1 (2 to 14)	−0.32 to 1.33	0.72
Noninvasive respiratory support	5.2 (3 to 13)	4.8 (2 to 13)	−0.25 to 1.06	0.31
Oxygen supplementation	0.4 (0 to 3)	0.3 (0 to 3)	−0.19 to 0.38	0.26
Caffeine treatment	3.2 (0 to 24)	2.0 (0 to 22)	−0.23 to 2.51	0.68
Surfactant, number (%)	25 (38.5)	27 (42.9)	0.41 to 1.69	0.61
Air leaks	2 (3.1)	1 (1.6)	0.17 to 22.3	0.58
BPD	6 (9.2)	6 (9.5)	0.29 to 3.2	0.96
Age at discharge, d	30.5 (14 to 55)	30.6 (16 to 49)	−4.08 to 3.86	0.96

BPD, bronchopulmonary dysplasia; HHHFNC, heated, humidified high-flow nasal cannula; IQR, interquartile range.

Table 4: Occurrence rates for secondary outcomes in the HHHFNC compared with the NCPAP study group.

Outcome	HHHFNC ($n = 65$)	NCPAP ($n = 63$)	95% CI of risk difference	P value
Adverse event, number (%)				
Confirmed sepsis	5 (7.7)	7 (11.1)	0.20 to 2.22	0.51
IVH	3 (4.6)	2 (3.2)	0.24 to 9.14	0.67
PDA	4 (6.2)	4 (6.3)	0.23 to 4.05	0.96
ROP	3 (4.6)	2 (3.2)	0.24 to 9.14	0.67
nasal trauma	14 (21.5)	27 (42.9)	0.17 to 0.79	0.01
Death	1 (1.5)	1 (1.6)	0.06 to 16.08	0.99
Abdominal distention	7 (10.8)	8 (12.7)	0.28 to 2.44	0.73
Days to full oral feedings, median (IQR), d	11.1 (5–20)	11.5 (5–24)	−2.30 to 1.50	0.68
Exclusive breastfeeding at discharge, number (%)	12 (18.5)	10 (15.9)	0.48 to 3.02	0.70
Weight at discharge, median (IQR), g	2150 (2000 to 2450)	2176 (2050 to 2550)	−73.5 to 22.5	0.30

oxygen. Finally, we found that HHHFNC was associated with less nasal trauma than NCPAP.

Noninvasive respiratory support including NCPAP and HHHFNC [8] is considered the optimal method of providing assistance to preterm babies with breathing problems. HHHFNC has gained popularity all over the world in the recent years. The 2015 survey of UK [9] shows that the use of HHHFNC significantly increased in 2015 (87%) compared with 2012 (56%). There is insufficient evidence about the safety and efficacy of HHHFNC in low- and middle-income countries. Most studies investigated the heated humidified high-flow nasal cannula for the prevention of extubation failure in neonates [10–13]. The evidence of respiratory support of HHHNFC as primary mode after birth in preterm infants is rare [14–16]. Lavizzari et al. [14] conducted a large RCT on HHHFNC versus NCPAP in infants between 29 and 36 weeks' GA as primary therapy to mild to moderate RDS in preterm infants. In their study, HHHFNC showed efficacy and safety similar to those of NCPAP when applied as a primary approach to mild to moderate RDS in preterm infants older than 28 weeks' GA. Despite the different study design and lower percentages of infants less than 32 weeks and less than 1500 g in our study ($P = 0.05$, $P = 0.126$), in agreement with Lavizzari's RCT [14], we draw the same conclusion that HHHFNC is an effective and well-tolerated strategy that could be as effective as NCPAP as the primary treatment of mild to moderate RDS in preterm infants older than 28 weeks' GA. On the contrary, the HIPSTER study [17] showed that high-flow therapy resulted in a significantly higher rate of treatment failure than NCPAP when used as primary support for preterm infants with respiratory distress. However, there is significant difference between two studies in the baseline characteristics of the study population including the proportion of gestational age < 32 weeks: 51.2% in the HIPSTER study versus 32.8% in our study, respectively. This indicates that the more mature preterm infants may tolerate HHHFNC better as the primary support for preterm infants. But higher failure rates occurred in our study, because of the low rate of prenatal steroids and caffeine treatment. Another reason might be that the time of treatment failure of our study is within 7 days instead of 72 hours. The rate of neonatal resuscitation was also higher (~58%) in these relatively large infants in our study because the rate of prenatal steroids was relatively low (38.3%), which is the routine in middle-income countries. In agreement with the previous large RCTs on HHHFNC [14, 17], we did not find any difference in the rate of sepsis when compared with NCPAP.

The model of respiratory support of HHHFNC was studied as a main mode of respiratory support in the delivery room [18]. Heated, humidified high-flow nasal cannulas (HHHFNC) are small, thin, tapered binasal tubes that deliver oxygen or blended oxygen/air at gas flows of more than 1 L/min [5]. Although HHHFNC is a relatively simple device, an important drawback is the inability to be certain of the

delivered airway distending pressure [19]. The primary safety concern with HHHFNC is the potential for high, unmeasured distending pressures. In an in vitro model, Sivieri et al. recorded pressures up to 20–30 cm H_2O with flow rates >2 L/min [20]. The pressure generated in HHHFNC was not measured during this study. There are also concerns about the potential of infection in the use of HHHFNC [21]. Despite these drawbacks, we found a low rate of air leaks in the group of HHHFNC similar to previous studies ($P = 0.58$) [16, 22]. Similar to the study of De Klerk [23], we found that HHHFNC are smaller and lighter and typically utilize short, nonocclusive binasal prongs and require use of a heated water humidifier to prevent nasal trauma. But the rate of nasal trauma was relatively high in both groups in our study as compared to the current literature [10, 17], and this may be related to the limited number of paediatricians and nurses in China. China Health Statistics Almanac and World Health Statistics estimate that China had only 0.43 paediatricians for every 1000 children in 2012 and 2.05 nurses per 1000 population in 2013, well below the world average of 2.86 nurses [24]. The average doctor-to-nurse ratio in our hospital surveyed was 1 : 1.6, and the average bed-to-nurse ratio was 1 : 0.6. The average doctor-to-nurse and bed-to-nurse ratio in the NICU in our hospitals surveyed were significantly lower than the Ministry of Health standard, indicating a serious nursing shortage in the NICU. The shortages are exacerbated by a high turnover rate of staff caused by heavy workloads, deteriorating doctor-patient relationships, and increased work related stress. The study of Wilkinson et al. [5] shows that the popularity of HHHFNC seems to be due to other perceived advantages; for example, the cannulas are easier to apply than NCPAP prongs, may be more comfortable for infants, may be associated with less nasal trauma, and may enable easier access to babies' faces, thus allowing for greater opportunities for feeding and parental bonding.

Our study had some limitations. It was a monocentric rather than multicentric RCT. The mode of support assignment could not be blinded to the medical team. Using objective failure criteria and management protocols reduces the possibility of a bias that this might have caused. On the basis of data from our center, we estimated that treatment failure within 7 days would occur in 17.5% of infants assigned to receive NCPAP. We preestablish a noninferiority margin for high-flow treatment of 10 percentage points above the failure rate for NCPAP treatment. High-flow therapy would be considered noninferior to NCPAP if the difference in the risk of treatment failure and the upper limit of the two-sided 95% confidence interval were less than 10% and the lower limit of the 95% confidence interval was below zero. For the study to have 90% power, a sample of 760 infants would be required. Thus, it is possible that our study was underpowered. The sample size of our study population may not have been large enough to completely rule out a beneficial effect of either mode of nasal support (type II error). The safety conclusions from our study should also be taken with caution because of small sample size, as our study did not have sufficient statistical power to detect differences in relatively infrequent complications such as air leak, NEC, PDA, and IVH. The study was underpowered for superiority but equivalence was found. Although this study is limited by its relatively small size, the data presented here indicate that HHHFNC may represent a similarly well-tolerated and effective alternative respiratory support mode to NCPAP in the preterm infant population with mild to moderate RDS. Its potential advantages include its simplicity, improved tolerability with less injury to the nasal architecture and mucosa, and perhaps greater clinical utility in managing respiratory distress in premature infants in middle-income countries.

We believe our experience calls for a large multicenter randomized controlled trial comparing the efficacy, safety, and cost-benefit of HHHFNC to NCPAP in China in the future.

6. Conclusion

Our study shows that HHHFNC is an effective and well-tolerated strategy that could be as effective as NCPAP as the primary treatment of mild to moderate RDS in preterm infants between 28^{+0} and 34^{+6} weeks' GA. Multicenter randomized clinical trials should be conducted to verify our findings concerning the use of HHHFNC as primary respiratory support for preterm infants with RDS in low- and middle-income countries in the future.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Ge Zheng and Xiao-qiu Huang collected data, drafted the manuscript, and participated in the study. Hui-hui Zhao and Guo-Xing Jin participated in patients recruiting and collection and analysis and interpretation of data. Bin Wang designed and coordinated the study and made the decision to submit. All authors read and approved the final manuscript.

Acknowledgments

The authors would like to thank the staff of NICU in Ruian People's Hospital for their work.

References

[1] D. G. Sweet, V. Carnielli, G. Greisen et al., "European consensus guidelines on the management of respiratory distress syndrome—2016 update," *Neonatology*, vol. 111, no. 2, pp. 107–125, 2016.

[2] M. Armfield and G. West, "Use of Vapotherm for respiratory support with neonates," *Paediatric Nursing*, vol. 21, no. 1, pp. 27–30, 2009.

[3] N. Fleeman, J. Mahon, V. Bates et al., "The clinical effectiveness and cost-effectiveness of heated humidified high-flow nasal cannula compared with usual care for preterm infants: systematic review and economic evaluation," *Health Technology Assessment*, vol. 20, no. 30, pp. 1–68, 2016.

[4] B. J. Manley and L. S. Owen, "High-flow nasal cannula: mechanisms, evidence and recommendations," *Seminars in Fetal and Neonatal Medicine*, vol. 21, no. 3, pp. 139–145, 2016.

[5] D. Wilkinson, C. Andersen, C. P. O'Donnell, and A. G. De Paoli, "High flow nasal cannula for respiratory support in preterm infants," *Cochrane Database of Systematic Reviews*, vol. 5, Article ID CD006405, 2011.

[6] . Wyllie J, JM. Perlman, J. Kattwinkel, MH. Wyckoff, K. Aziz, and R. Guinsburg, "Neonatal Resuscitation Chapter Collaborators. Part 7: Neonatal Resuscitation," in *International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation, 2015*, supplement 1, pp. S204–41, 2015.

[7] D. G. Sweet, V. Carnielli, G. Greisen et al., "European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants—2013 update," *Neonatology*, vol. 103, no. 4, pp. 353–368, 2013.

[8] E. A. Jensen, A. Chaudhary, Z. A. Bhutta, and H. Kirpalani, "Non-invasive respiratory support for infants in low- and middle-income countries," *Seminars in Fetal and Neonatal Medicine*, vol. 21, no. 3, pp. 181–188, 2016.

[9] S. Shetty, A. Sundaresan, K. Hunt, P. Desai, and A. Greenough, "Changes in the use of humidified high flow nasal cannula oxygen," *Archives of Disease in Childhood: Fetal and Neonatal Edition*, vol. 101, no. 4, pp. F371–F372, 2016.

[10] C. L. Collins, J. R. Holberton, C. Barfield, and P. G. Davis, "A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants," *Journal of Pediatrics*, vol. 162, no. 5, pp. 949–954.e1, 2013.

[11] B. J. Manley, L. S. Owen, L. W. Doyle et al., "High-flow nasal cannulae in very preterm infants after extubation," *New England Journal of Medicine*, vol. 369, no. 15, pp. 1425–1433, 2013.

[12] S. Soonsawad, N. Tongsawang, and P. Nuntnarumit, "Heated humidified high-flow nasal cannula for weaning from continuous positive airway pressure in preterm infants: a randomized controlled trial," *Neonatology*, vol. 110, no. 3, pp. 204–209, 2016.

[13] Collaborative Group for the Multicenter Study on Heated Humidified High-Flow Nasal Cannula Ventilation, "Efficacy and safety of heated humidified high-flow nasal cannula for prevention of extubation failure in neonates," *Zhonghua Er Ke Za Zhi*, vol. 52, no. 4, pp. 271–276, 2014.

[14] A. Lavizzari, M. Colnaghi, F. Ciuffini et al., "Notice of Duplicate Publication: heated, humidified high-flow nasal cannula vs nasal continuous positive airway pressure for respiratory distress syndrome of prematurity: a randomized clinical non-inferiority trial," *JAMA Pediatrics*, vol. 170, no. 12, p. 1228, 2016.

[15] C. T. Roberts, L. S. Owen, B. J. Manley, S. M. Donath, and P. G. Davis, "A multicentre, randomised controlled, non-inferiority trial, comparing High flow therapy with nasal continuous positive airway pressure as primary support for preterm infants with respiratory distress (the HIPSTER trial): study protocol," *BMJ Open*, vol. 5, no. 6, Article ID e008483, 2015.

[16] B. A. Yoder, R. A. Stoddard, M. Li, J. King, D. R. Dirnberger, and S. Abbasi, "Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates," *Pediatrics*, vol. 131, no. 5, pp. e1482–e1490, 2013.

[17] C. T. Roberts, L. S. Owen, B. J. Manley et al., "Nasal high-flow therapy for primary respiratory support in preterm infants," *The New England Journal of Medicine*, vol. 375, no. 12, pp. 1142–1151, 2016.

[18] P. Reynolds, S. Leontiadi, T. Lawson, T. Otunla, O. Ejiwumi, and N. Holland, "Stabilisation of premature infants in the delivery room with nasal high flow," *Archives of Disease in Childhood: Fetal and Neonatal Edition*, vol. 101, no. 4, pp. F284–F287, 2016.

[19] J. J. Cummings and R. A. Polin, "Noninvasive respiratory support," *Pediatrics*, vol. 137, no. 1, 2016.

[20] E. M. Sivieri, J. S. Gerdes, and S. Abbasi, "Effect of HFNC flow rate, cannula size, and nares diameter on generated airway pressures: an in vitro study," *Pediatric Pulmonology*, vol. 48, no. 5, pp. 506–514, 2013.

[21] C. L. Collins, C. Barfield, R. S. C. Horne, and P. G. Davis, "A comparison of nasal trauma in preterm infants extubated to either heated humidified high-flow nasal cannulae or nasal continuous positive airway pressure," *European Journal of Pediatrics*, vol. 173, no. 2, pp. 181–186, 2014.

[22] Q. Wu, L. Zhao, and X. Ye, "Shortage of healthcare professionals in China," *BMJ*, vol. 354, p. i4860, 2016.

[23] A. De Klerk, "Humidified high-flow nasal cannula: is it the new and improved CPAP?" *Advances in Neonatal Care*, vol. 8, no. 2, pp. 98–106, 2008.

[24] A. Kugelman, A. Riskin, W. Said, I. Shoris, F. Mor, and D. Bader, "A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS," *Pediatric Pulmonology*, vol. 50, no. 6, pp. 576–583, 2015.

Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 1783857, 10 pages
https://doi.org/10.1155/2017/1783857

Review Article

Mechanical Ventilation during Extracorporeal Membrane Oxygenation in Patients with Acute Severe Respiratory Failure

Zhongheng Zhang,[1] Wan-Jie Gu,[2] Kun Chen,[3] and Hongying Ni[3]

[1]*Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, China*
[2]*Department of Anesthesiology, Nanjing Drum Tower Hospital, Medical College of Nanjing University, Nanjing 210008, China*
[3]*Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Zhejiang, China*

Correspondence should be addressed to Zhongheng Zhang; zh_zhang1984@hotmail.com

Received 26 August 2016; Revised 28 November 2016; Accepted 18 December 2016; Published 3 January 2017

Academic Editor: Angelo G. Corsico

Conventionally, a substantial number of patients with acute respiratory failure require mechanical ventilation (MV) to avert catastrophe of hypoxemia and hypercapnia. However, mechanical ventilation per se can cause lung injury, accelerating the disease progression. Extracorporeal membrane oxygenation (ECMO) provides an alternative to rescue patients with severe respiratory failure that conventional mechanical ventilation fails to maintain adequate gas exchange. The physiology behind ECMO and its interaction with MV were reviewed. Next, we discussed the timing of ECMO initiation based on the risks and benefits of ECMO. During the running of ECMO, the protective ventilation strategy can be employed without worrying about catastrophic hypoxemia and carbon dioxide retention. There is a large body of evidence showing that protective ventilation with low tidal volume, high positive end-expiratory pressure, and prone positioning can provide benefits on mortality outcome. More recently, there is an increasing popularity on the use of awake and spontaneous breathing for patients undergoing ECMO, which is thought to be beneficial in terms of rehabilitation.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is an important technique for the treatment of severe respiratory failure, providing opportunity for lung recovery or transplantation [1, 2]. Hill and colleagues first described ECMO support for cases of severe respiratory failure four decades ago [3]. Since then, a large number of observational studies and randomized trials have been performed [4, 5]. In common practice, ECMO is indicated when conventional mechanical ventilation fails to improve arterial oxygenation and/or eliminate carbon dioxide [6]. Another indication is the circulatory and/or cardiac failure. However, ECMO has not been well established (e.g., in the framework of evidence based medicine) for its effectiveness in the treatment severe respiratory failure, especially in some particular situations such as immune-compromised patients [7]. While there is uncertainty on the effectiveness of ECMO versus mechanical ventilation on mortality outcome, ECMO is still widely used for patients with refractory respiratory failure.

Because ECMO is expansive, is technically challenging, and bears catastrophic complications, it is not considered as a first line therapy for patients with respiratory failure [8]. A typical therapeutic protocol of severe acute respiratory distress syndrome (ARDS) is shown in Figure 1 [9]. The first line therapy (step 1) for severe ARDS is mechanical ventilation with a variety of modes [10–13]. Protective ventilation is typically employed. If the patient responds poorly to the initial MV setting, the strategy is to initiate VV-ECMO with the therapeutic target to maintain SaO_2 and serum pH. Weaning off the ECMO is considered when the blood and gas flow are decreased to 2 L/min and 21%, respectively [9]. During ECMO running, mechanical ventilation is still in use. As a result, respiratory support of such patients comprises the native lung and artificial lung. The mechanical ventilation setting in patients undergoing ECMO is an area

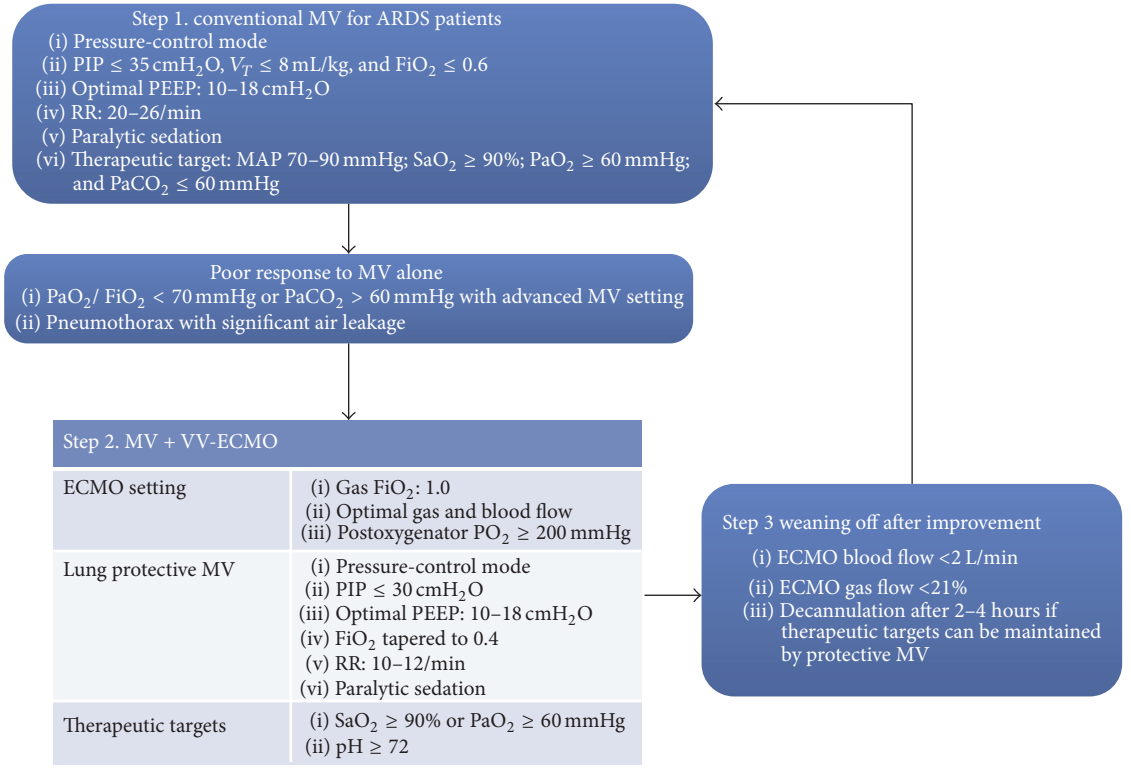


Figure 1: Management of severe acute respiratory distress syndrome in adults. Note that extracorporeal membrane oxygenation is provided after failure of conventional ventilation. Step 1 is the use of conventional MV for ARDS patients. Protective ventilation is typically employed. If the patient responds poorly to the initial MV setting, the strategy is to initiate VV-ECMO with the therapeutic target to maintain SaO_2 and serum pH. Weaning off the ECMO is considered when the blood and gas flow are decreased to 2 L/min and 21%, respectively. The figure was adapted from [9] under the Creative Commons Attribution License 4.0, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. MV: mechanical ventilation; VV-ECMO: venovenous extracorporeal membrane oxygenation; MAP: mean arterial pressure; PEEP: positive end-expiratory pressure; RR: respiratory rate.

of active research. There is controversy on the optimal degree of mechanical ventilation support. While ultra-protective ventilation provides enough lung rest, lung recruitment may accelerate lung recovery [14]. In the present review we summarize the current evidence on mechanical ventilation during ECMO.

2. Physiology behind ECMO

Because this review primarily focuses on mechanical ventilation during ECMO, we first need to understand some physiological changes during ECMO. Venovenous extracorporeal membrane oxygenation (VV-ECMO) is commonly used for the management of patients with respiratory failure and stable hemodynamics. The venous blood with low oxygen saturation (SvO_2) is typically drained from superior vena cava, inferior vena cava, and/or large vein such as femoral or subclavian vein. It passes through the oxygenator [15] and then returns to the patient in or near the right atrium [16]. The returned blood with high oxygen content is mixed with systemic venous blood and enters into right heart. The mixed venous blood is further oxygenated in the native lung. However, due to low mechanical ventilation setting, such oxygenation is always negligible. Mechanical ventilation in this regard is more to keep the lung open than to provide oxygen [16]. However, native lung function is not always negligible; this may be the case for native lung CO_2 removal. Respiratory drive cannot be fully controlled by extracorporeal CO_2 removal, especially in acute hypoxemic patients.

Because ECMO is able to provide oxygen and remove carbon dioxide, the respiratory drive and effort can be controlled. A few animal studies showed that carbon dioxide removal by ECMO was able to induce apnea [17, 18]. In human study, when gas flow (e.g., control of carbon dioxide) dropped from 100% to 0%, pressure generated in the first 100 ms of inspiration against an occluded airway increased from 0.9 ± 0.5 to 2.8 ± 2.7 cmH_2O ($p < 0.001$); the maximal inspiratory muscles pressure increased from 4.5 ± 3.1 to 8.5 ± 6.3 cmH_2O. The authors concluded that carbon dioxide removal had significant impact on spontaneous breathing effort [19].

An important feature of VV-ECMO is its mild hemodynamic effect on circulation. This is of particular importance for hemodynamically unstable patients with acute respiratory failure (ARF). In animal models, Shen and colleagues found that although there were mild changes in ultrastructure and function of cardiomyocyte and mitochondria, the global

hemodynamics were stable [20]. Also, there is evidence that the installation of VV-ECMO decreases heart rate, but mean arterial pressure is not significantly affected [21]. Given the favorable hemodynamic features of VV-ECMO, it can be used for patients with hemodynamically unstable patients. However, if a patient shows ARF in combination with refractory shock, venoarterial ECMO (VA-ECMO) should be recommended for use.

3. Timing of ECMO Initiation: Indications from Ventilation Parameters

Because mechanical ventilation typically precedes ECMO and mechanical ventilation parameters provide important information for the initiation of ECMO, in this section, we discuss when to start ECMO for severe respiratory failure.

The principle to start ECMO is when conventional mechanical ventilation cannot provide enough oxygenation and/or carbon dioxide elimination or ventilator setting is too high that can cause significant lung injury. Another condition is that the duration of mechanical ventilation is not too long that the underlying pathology is reversible. The timing of ECMO is usually based on the severity of ARDS, as represented by severe hypoxemia despite high PEEP (PaO_2/FiO_2 < 80 mmHg) and uncompensated hypercapnia (pH < 7.2) [22]. There is evidence that early initiation of ECMO (1.9 ± 1.4 days after onset of severe ARDS defined by Berlin definition) improves survival in trauma patients [23]. However, this study is limited by small sample size and the use of historical control. A large randomized controlled trial conducted by Peek and colleagues was probably the cornerstone in exploring the indications of ECMO for ARDS patients [24]. In the study, ARDS patients with Murray score > 3.0 or pH < 7.20 were randomized to receive either ECMO or conventional mechanical ventilation. The 6-month survival was 63% in the ECMO group versus 47% in the control group ($p = 0.03$). With the success of this trial, the criteria were adopted by Italian ECMO network. Use of the criteria in ARDS patients caused by influenza A (H1N1) virus showed a survival discharge rate of 68% [25]. In a well-matched cohort, early VV-ECMO was associated with lower mortality in patients with severe hypoxemic respiratory failure [26]. A threshold of plateau pressure is commonly used to avoid lung injury during mechanical ventilation. However, plateau pressure is generated by elastances of the lung and chest wall. It is the transpulmonary pressure that can cause lung injury. Grasso and colleagues reported ECMO initiation criteria using transpulmonary pressure estimated with esophageal pressure. In 14 patients with influenza A-(H1N1-) associated ARDS referred for ECMO, half of them avoided ECMO when upper limit of transpulmonary pressure equal to 25 cmH_2O was employed [27].

There are also situations in which the use of ECMO may not be beneficial. In terms of mechanical ventilation, it was suggested that patients on mechanical ventilation for over 7 days were contraindicated for ECMO [24]. While it is well known that prolonged mechanical ventilation is a harbinger of adverse outcome, the days are not well established by empirical evidence. For example, Cheng and colleagues developed a VV-ECMO mortality score to triage patients before ECMO running, in which Pre-ECMO MV day > 4 was the most important predictor of death with a coefficient of 2 (i.e., other predictors had coefficient of 1) [28]. Other observational studies also identified similar relationship between Pre-ECMO MV days and mortality outcome [9, 29–31]. Most importantly, MV prior to initiation of ECMO is an important component in the calculation of Respiratory ECMO Survival Prediction (RESP) score. This score has been validated to assist prediction of survival for adult patients undergoing ECMO for respiratory failure [4, 32]. However, it is still difficult to determine a specific time point after which the initiation of ECMO can be considered futile. Probably, this is dependent on the sophistication of individual centers, and here individualized selection of patients should be performed.

4. Protective Ventilation in ECMO

It is well understood that conventional ventilation mode can cause ventilator induced lung injury (VILI). The underlying mechanisms of VILI include alveolar overdistension (volutrauma), alveolar instability leading to alveolar collapse and reopening with each breath (atelectrauma), and the secondary inflammation caused by these mechanical injuries which is known as biotrauma [33]. Volutrauma is caused by ventilation at high tidal volumes. The effect of ventilation volumes on injury is independent of the peak airway pressure. Rat models have shown that, at the same peak airway pressure (45 cmH_2O), those ventilated with low tidal volumes developed less severe permeability and pulmonary edema [34]. In clinical practice, ventilation at high airway pressure is observed to cause lung injury manifested as pneumothorax or subcutaneous emphysema. However, since the high airway pressures per se do not cause VILI unless they are associated with high lung volumes, the term barotrauma is a misnomer [35]. To ameliorate the VILI, the concept of protective MV is introduced into clinical practice. The following paragraphs examine the use of protective ventilation in patients undergoing ECMO.

Protective ventilation with low tidal volume has long been known as a major component of ventilation strategy for both injured and healthy lung [10, 36, 37]. A landmark study on low tidal volume ventilation was conducted nearly two decades ago [38]. The study showed that patients who received protective ventilation versus conventional group had significantly lower 28-day mortality rate (38% versus 71%; $p < 0.001$). A recent network meta-analysis showed that ventilation with low tidal volume plus prone position was associated with reduced risk of death (hazards ratio: 0.62; 95% CI: 0.42–0.98) [39]. However, some studies failed to identify a beneficial effect on mortality [40, 41] or the effect size is much less than that in Amato's study [42]. While the benefit of low tidal volume ventilation is to reduce lung injury, it may cause carbon dioxide retention and hypoxemia due to reduced ventilation. In other words, the balance between lung rest and working is difficult to determine. Patient population with severe ARDS is actually an extremely heterogeneous group that one size does not fit all, and the relative importance

of lung rest versus metabolic demand can be different across the population. During VV-ECMO, mechanical ventilation is still required due to reasons that (1) ECMO blood flow rate is usually not enough and in hyperdynamic status a substantial proportion of blood still passed via native lung, not having gone through the artificial lung first; (2) lung should be mildly ventilated and kept open. Complete collapse of the lung may delay its recovery. There is evidence that a sufficient PEEP level is beneficial [43].

The major obstacle for performing low tidal volume ventilation is carbon dioxide retention, worsened oxygenation, and intrapulmonary shunt [44]. When tidal volume reduces below 6 mL/kg, arterial $PaCO_2$ level increased remarkably and the pH value dropped below 7.2. Such a procedure for lung rest is performed at the cost of metabolic disturbances and tissue hypoxia. Fortunately, ECMO can provide an opportunity for the lung to rest while maintaining tissue oxygen supply and carbon dioxide elimination. With extracorporeal carbon dioxide removal, Ranieri and colleagues showed that tidal volume < 6 mL/kg enhanced lung protection with respect to acid-base homeostasis, cytokine secretion, and pulmonary morphology [45]. Thus, it is wise to rest the lung in severe ARDS patients who are also supported with ECMO. In an international survey on ventilator setting during ECMO, 77% of ECMO centers reported "lung rest" as the primary goal of mechanical ventilation; a tidal volume of 6 mL/kg or less was targeted in 76% centers [46]. Although there is a lack of randomized controlled trial in this topic, there is a large body of observational evidence supporting the notion that protective ventilation is associated with better outcome [47]. In Schmidt et al.'s study, protective ventilation was routinely used in high-volume ECMO centers. Higher positive end-expiratory pressure levels during the first 3 days of ECMO support were associated with lower mortality (odds ratio, 0.75; 95% CI, 0.64–0.88; $p = 0.0006$) [43]. With multivariable regression model, it was found that each one cmH_2O increase in plateau pressure was associated with a 14.4% decrease in the odds of achieving hospital survival (95% CI = 1.75% to 25.4%, $p = 0.027$). Conversely, each one cmH_2O increase in PEEP was associated with a 36.2% decrease in the odds of 30-day survival (95% CI = 10.8% to 54.4%, $p = 0.009$) [48]. Pandemic influenza A is a tragedy for human being, but it provides a good opportunity for exploring mechanical ventilator setting in ECMO patients [49]. Survivors had significantly lower plateau pressure during ECMO than nonsurvivors (25 ± 3 versus 29 ± 5 cmH_2O; $p < 0.01$). The result remained unchanged even after multivariable adjustment (OR: 1.33; 95% CI: 1.14–1.59; $p < 0.01$). More recently, some authors also explored the use of ultra-protective ventilation (i.e., tidal volume reduced to 4 mL/kg predicted body weight while PEEP was increased to target a plateau pressure between 23 and 25 cmH_2O) with the help of low-flow extracorporeal carbon dioxide removal ($ECCO_2R$) in moderate ARDS [50].

Another component of protective ventilation is low respiratory rate [51]. The rationale of this procedure is to rest the lung by reducing its motion. The lungs were ventilated 3 to 5 times per minute, with peak airway pressure limited to 35 to 45 cmH_2O. A continuous oxygen flow was provided. Carbon dioxide elimination was performed by extracorporeal method [51].

Closed-loop ventilation represents another novel protective ventilation mode [52]. It automatically adjusts some settings according to physiological target made by physicians, making it possible to select an individualized ventilator setting [53]. IntelliVent-ASV™ is an extension and development of adaptive support ventilation (ASV) that automatically adjusts ventilation settings such as minute volume, tidal volume (VT), and respiratory rate (RR), to reach a target end-tidal CO_2 ($PETCO_2$) in passively breathing patients and a target RR in actively breathing patients. Furthermore, inspiratory fraction of oxygen (FiO_2) and positive end-expiratory pressure (PEEP) are adjusted automatically to reach a target pulse oximetry (SpO_2). Although the closed-loop ventilation mode has been shown to be safe and effective in patients with ARDS, its use in patients undergoing ECMO has not been fully investigated [54, 55]. In a case series involving six patients, Karagiannidis and colleagues reported that closed-loop ventilation mode responded rapidly to decreased ECMO sweep gas flow. It concluded that the combination of neurally adjusted ventilatory assist (NAVA) and ECMO might permit a closed-loop ventilation with automated protective ventilation [56].

5. Recruitment Maneuvers

Recruitment maneuver is the indispensable component of protective ventilation, and there are a variety of methods to perform recruitment maneuver. In this section, we aimed to describe some commonly used recruitment maneuvers. Grasso and colleagues proposed the titration of PEEP according to stress index. Stress index (b) can be estimated based on airway pressure and inspiratory time by the following equation:

$$\text{Airway pressure} = a \cdot \text{Inspiratory time}^{b} + c, \quad (1)$$

where the coefficient b is the stress index describing the shape of the airway opening pressure (Pao) corresponding to the period of constant-flow inflation. For $b < 1$, the Pao curve presents a downward concavity, suggesting a continuous decrease in elastance during constant-flow inflation. For $b > 1$, the curve presents an upward concavity suggesting a continuous increase in elastance. For $b = 1$, the curve is straight, suggesting the absence of tidal variations in elastance. PEEP level was titrated to target a stress index between 0.9 and 1.1 [57]. Specifically, PEEP was decreased if the stress index was higher than 1.1 and was increased if the stress index was lower than 0.9. PEEP is not changed if the stress index was between 0.9 and 1.1 [58].

Talmor and colleagues proposed to set PEEP levels in reference to the esophageal pressure. Patients underwent heavy sedation and paralysis. Recruitment maneuver was performed by increasing airway pressure to 40 cmH_2O for 30 seconds. Thereafter, PEEP was set to achieve a transpulmonary pressure of 0 to 10 cmH_2O at end expiration, according to a sliding scale based on the PaO_2 and the FiO_2 (Table 1) [59]. Ventilator setting was adjusted in one column at a time

Table 1: Sliding scale of esophageal pressure-guided titration of PEEP. The table was adapted from [59]. Ventilator setting is adjusted in one column at a time to keep the partial pressure of arterial oxygen (PaO_2) between 55 and 120 mmHg. Alternatively, the oxygen saturation, as measured by pulse oximeter, is kept between 88 and 98% by using the ventilator settings in one column at a time. The positive end-expiratory pressure (PEEP) is set at such a level that transpulmonary pressure during end-expiratory occlusion (PLexp) stays between 0 and 10 cmH_2O and keeps transpulmonary pressure during end-inspiratory occlusion at less than 25 cmH_2O.

FiO_2	0.4	0.5	0.5	0.6	0.6	0.7	0.7	0.8	0.8	0.9	0.9	1.0
Plexp	0	0	2	2	4	4	6	6	8	8	10	10

to keep the partial pressure of arterial oxygen (PaO_2) between 55 and 120 mmHg. Alternatively, the oxygen saturation, as measured by pulse oximeter, was kept between 88 and 98% by using the ventilator settings in one column at a time. The PEEP was set at such a level that transpulmonary pressure during end-expiratory occlusion (PLexp) stays between 0 and 10 cmH_2O and keeps transpulmonary pressure during end-inspiratory occlusion at less than 25 cmH_2O. Tidal volume was set at 6 mL/kg of predicted body weight. The predicted body weight was estimated using the following equation:

$$\begin{aligned}\text{Predicted body weight} &= 50\,(\text{if male}, 45.5\ \text{if female}) + 0.91 \\ &\times (\text{centimeters of height} - 152.4).\end{aligned} \quad (2)$$

In the EXPRESS trial, "open-lung approach" was employed to treat patients with severe ARDS [60]. The ventilator procedures included pressure-control mode, targeting tidal volume of 6 mL/kg of predicted body weight, and plateau airway pressures less than 40 cmH_2O. The recruitment maneuver included a 40-second breath-hold at an airway pressure of 40 cmH_2O and an FIO_2 of 1.0. Oxygenation was maintained in a target range as described previously using a slide scale of PEEP/FiO_2 combinations (Table 2) [42].

6. Prone Positioning of Patients during ECMO

Prone position is an alternative or rescue therapy for patients with severe ARDS. Prone positioning may help to reduce collapse of dorsal lung segments with subsequent avoidance of alveolar overdistension of ventral lung segments. The aim is to homogenize transpulmonary pressure and reduce intrapulmonary shunt. In patients with severe ARDS, prone positioning has been proven to be beneficial in some clinical outcomes such as mortality (relative risk [RR]: 0.9; 95% CI: 0.82–0.98) [61], ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (63.0 ± 66.8 versus 44.6 ± 68.2, $p = 0.02$) [62], and ventilator-associated pneumonia (1.66 versus 2.14 episodes per 100 patients-days of intubation; $p = 0.045$) [63]. The well-known PROSEVA study is the largest multicenter study investigating the effect of prone positioning on mortality outcome. The study confirmed that early application of prolonged prone positioning sessions significantly decreased 28-day (16.0% versus 32.8%; $p < 0.001$) and 90-day mortality (23.6% versus 41.0%; $p < 0.001$) in patients with severe ARDS [64].

Prone positioning can be successfully performed during ECMO, and it is associated with improved respiratory parameters. In 17 subjects undergoing VV-ECMO who also failed at least one weaning attempt, prolonged prone positioning (24 hours) was performed [65]. Respiratory system compliance increased from 18 (12–36) to 32 (15–36) mL/cmH_2O ($p < 0.0001$), and the PaO_2/FiO_2 ratio increased from 111 (84–128) to 173 (120–203) mmHg ($p < 0.0001$). Similar findings were reported in several case series and observational cohort studies [66–69]. Indications of prone positioning during ECMO include difficult-to-wean, severe hypoxia ($PaO_2/FiO_2 < 70$) and injurious ventilator setting with plateau pressure exceeding 32 cmH_2O [70].

One challenging issue in performing prone positioning is the potential risk of turning the patient. Thus, some authors propose that ECMO may be a relative contraindication of prone positioning [67]. Reported adverse effects include cannula malfunction, inadvertent extubation, bed sore, and dislodged arterial and central venous lines [71]. Cannula and chest tube site bleedings were also noted in some studies [72, 73]. A standard turning procedure should be protocolized in specialized centers to avoid these potentially detrimental events. There is evidence that prone positioning during ECMO is safe if performed properly [74, 75].

7. Spontaneous Breathing during ECMO

Spontaneous breathing is usually not allowed during early phase of severe ARDS, mostly because these critically ill patients require protective ventilation (e.g., low tidal volume, high positive end-expiratory pressure, and recruitment maneuver) [76]. To perform protective ventilation, patients usually require deep sedation and paralysis. In ACURASYS (ARDS et Curarisation Systematique) trial, the use of neuromuscular blocking agents to suppress spontaneous breathing was found to be beneficial on clinical important outcomes such as ICU-free days and mortality (hazard ratio at 90 days: 0.68; 95% CI: 0.48–0.98). The effect was statistically significant in severe ARDS (90-day mortality: 30.8% versus 44.6%, $p = 0.04$) [77]. Similar results have been reported in other studies [78–82]. However, adverse effects of deep sedation and paralysis, including bradycardia, ICU-acquired paresis, ventilator-associated pneumonia, are still important concerns. To avoid potential adverse effects of deep sedation and paralysis, some pioneering centers start to use ECMO as the first line therapy, rather than rescue therapy after MV failure. Thus, there is accumulating evidence on the use of ECMO in awake, spontaneously breathing patients [83–85]. In patients waiting for lung transplantation, those underwent ECMO with spontaneous breathing demonstrated improved survival when compared to other bridging strategies [84].

ECMO may provide an alternative to deliver protective ventilation. As previously mentioned, carbon dioxide removal is able to control spontaneous breathing effort. With more carbon dioxide removal by increasing gas and blood flow, apnea can be induced in animals [17, 18]. Similar results

Table 2: Sliding scale of PEEP/FiO_2 combinations to maintain oxygenation. Positive end-expiratory pressure (PEEP) represents the level set at ventilator and not levels of total PEEP, auto-PEEP, or intrinsic PEEP.

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	20–24

have been found in human studies [19, 86]. In late phase of severe ARDS, spontaneous breathing can be allowed to prevent adverse impact of long-term controlled ventilation. For example, respiratory muscle atrophy is common in patients with prolonged mechanical ventilation, and the adverse effect can occur at as few as 18 hours after mechanical ventilation [87]. Restoration of respiratory muscle activity is helpful to decrease or prevent such disuse myopathy [88]. Another benefit of spontaneous breathing is its systemic and preportal organ blood flow. In an animal study, Hering and coworkers showed that the stomach blood flow increased from 0.13 ± 0.01 to 0.29 ± 0.05 mL/g·min with spontaneous breathing. Similar trends were found in other visceral organs [89]. It is well known that visceral organ perfusion is an important determinant of clinical outcomes in the critically ill. In a case series of six participants, Karagiannidis and colleagues found that patients could immediately regulate $PaCO_2$ towards a physiological range. Tidal volume was increased from 2–5 mL/kg to 8 mL/kg with inactivated ECMO, and inspiratory pressure increased from 19–29 cmH_2O to 21–45 cmH_2O [56]. Spontaneous breathing in severe ARDS animals undergoing ECMO support was associated with improved oxygenation and intrapulmonary shunt and redistributed ventilation towards dorsal areas, as compared to those with controlled ventilation [44]. The mechanical ventilation mode allowing for spontaneous breathing can be assisted mode, continuous positive airway pressure plus pressure support, and neural adjusted mechanical ventilation.

Furthermore, allowing spontaneous breathing during ECMO may be beneficial in terms of early rehabilitation, because these patients requires less sedation and paralysis. It is possible to perform early rehabilitation for this group of patients. In a study involving 100 ECMO patients, investigators found that 35% (35/100 patients receiving ECMO) could participate in early mobilization and that 51% (18/35) were able to walk [90]. Thus, early mobilization is considered safe and feasible. There is evidence that patients receiving physical training can have much shorter duration of ICU stay [91].

In aggregate, spontaneous breathing is not allowed at early phase of severe ARDS, aiming to perform protective ventilation. With ECMO support, there is no worrisome on hypoxemia and hypercapnia and protective ventilation can be easily delivered. At recovery phase of severe ARDS, it may be wise to lower the ECMO sweep gas and blood flows, allowing recovery of spontaneous breathing. The recovery can be very quick.

8. Weaning

Some authors proposed that weaning VV-ECMO should start with ventilator weaning. The procedure may begin when the patient was able to maintain adequate gas exchange with decreasing ECMO and sweep flow and minimal ventilator setting. Patients can be weaned from mechanical ventilation while still on ECMO therapy. The use of single-site, dual lumen catheter in the internal jugular vein allows extubated patients to be ambulatory while being connected to the ECMO circuit. Such a strategy requires a good teamwork among nurses, physicians, and other medical workers [92]. Thereafter, when the FiO_2 is weaned on ECMO, the flow rate can be decreased below 2.5 L/min. Decannulation can be considered when the patient is treated at lowest FiO_2 and ECMO flow.

Other authors prefer the use of a lung-protective MV approach and later decide to prioritize weaning VV-ECMO over MV [47]. In an international survey involving 141 individual responses, Marhong and colleagues reported that the majority of centers prioritized weaning VV-ECMO over mechanical ventilation [46]. The weaning protocol can be performed as recommended by extracorporeal life support organization (ELSO) guidelines (https://www.elso.org): ECMO flows are decreased in steps to a minimum of 1 L/min while maintaining sweep at 100%. Alternatively, the flows are decreased to 2 L/min and then the sweep FiO_2 is decreased. Both approaches should aim to maintain SaO_2 greater than 95%. When SaO_2 is stable on this setting, the sweep can be clamped on ventilator settings of pressure support ventilation (PSV) or continuous positive airway pressure (CPAP) of 20 cmH_2O. If $SaO_2 > 95\%$ and $PaCO_2 < 50$ mmHg can be maintained for 60 minutes, ECMO can be weaned.

9. Conclusions

Although MV is commonly employed to avert catastrophic hypoxemia and hypercapnia in patients with severe ARDS, MV per se can cause lung injury and accelerate the disease progression. Extracorporeal membrane oxygenation (ECMO) provides an alternative to rescue patients with severe respiratory failure that MV fails to maintain adequate gas exchange. The timing of ECMO initiation based on the risks and benefits of ECMO has been widely investigated. In the running of ECMO, the protective ventilation strategy can be employed without worrying about catastrophic hypoxemia and carbon dioxide retention. There is a large body of evidence showing that protective ventilation with low tidal volume, high PEEP, and prone positioning can provide benefits on mortality outcome. More recently, there is an increasing popularity on the use of awake and spontaneous breathing for patients undergoing ECMO. Lastly, we discussed ECMO weaning. The majority of centers prioritized weaning VV-ECMO over mechanical ventilation, while others preferred to wean MV first.

Competing Interests

There is no conflict of interest.

References

[1] G. Makdisi and I.-W. Wang, "Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology," *Journal of Thoracic Disease*, vol. 7, no. 7, pp. E166–E176, 2015.

[2] J. A. Hayanga, J. K. Aboagye, H. K. Hayanga, J. D. Luketich, and J. D'Cunha, "Extracorporeal membrane oxygenation as a bridge to lung re-transplantation: is there a role?" *The Journal of Heart and Lung Transplantation*, vol. 35, no. 7, pp. 901–905, 2016.

[3] J. D. Hill, T. G. O'Brien, J. J. Murray et al., "Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung," *New England Journal of Medicine*, vol. 286, no. 12, pp. 629–634, 1972.

[4] M. Schmidt, M. Bailey, J. Sheldrake et al., "Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The respiratory extracorporeal membrane oxygenation survival prediction (RESP) score," *American Journal of Respiratory and Critical Care Medicine*, vol. 189, no. 11, pp. 1374–1382, 2014.

[5] C. Karagiannidis, D. Brodie, S. Strassmann et al., "Extracorporeal membrane oxygenation: evolving epidemiology and mortality," *Intensive Care Medicine*, vol. 42, no. 5, pp. 889–896, 2016.

[6] E. C. Goligher, N. D. Ferguson, and L. J. Brochard, "Clinical challenges in mechanical ventilation," *The Lancet*, vol. 387, no. 10030, pp. 1856–1866, 2016.

[7] M. V. Dioverti, K. A. Cawcutt, G. J. Schears, and L. M. Baddour, "Use of extracorporeal membrane oxygenation for the treatment of influenza-induced acute respiratory distress syndrome in immunocompromised adults," *The American Journal of the Medical Sciences*, vol. 352, no. 1, pp. 81–85, 2016.

[8] R. M. Sweeney and D. F. McAuley, "Acute respiratory distress syndrome," *The Lancet*, vol. 388, no. 10058, pp. 2416–2430, 2016.

[9] M.-Y. Wu, C.-C. Huang, T.-I. Wu, C.-L. Wang, and P.-J. Lin, "Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome in adults: prognostic factors for outcomes," *Medicine*, vol. 95, no. 8, Article ID e2870, 2016.

[10] Y. Yu, C. Zhu, X. Qian, Y. Gao, and Z. Zhang, "Adult patient with pulmonary agenesis: focusing on one-lung ventilation during general anesthesia," *Journal of Thoracic Disease*, vol. 8, no. 1, pp. E124–E129, 2016.

[11] M. R. Tucci, E. L. Costa, M. A. Nakamura, and C. C. Morais, "Noninvasive ventilation for acute respiratory distress syndrome: the importance of ventilator settings," *Journal of Thoracic Disease*, vol. 8, no. 9, pp. E982–E986, 2016.

[12] C. Hodgson, E. C. Goligher, M. E. Young et al., "Recruitment manoeuvres for adults with acute respiratory distress syndrome receiving mechanical ventilation," *The Cochrane Database of Systematic Reviews*, vol. 11, Article ID CD006667, 2016.

[13] J. Li, H. Xu, M. Li, and J. Chen, "Effect of setting high APRV guided by expiratory inflection point of pressure-volume curve on oxygen delivery in canine models of severe acute respiratory distress syndrome," *Experimental and Therapeutic Medicine*, vol. 12, no. 3, pp. 1445–1449, 2016.

[14] G. Foti and A. Pesenti, "To recruit or not recruit, this is ...," *Critical Care Medicine*, vol. 43, no. 3, pp. 719–720, 2015.

[15] R. H. Bartlett, "Physiology of gas exchange during ECMO for respiratory failure," *Journal of Intensive Care Medicine*, In press.

[16] A. Sen, H. E. Callisen, C. M. Alwardt et al., "Adult venovenous extracorporeal membrane oxygenation for severe respiratory failure: current status and future perspectives," *Annals of Cardiac Anaesthesia*, vol. 19, no. 1, pp. 97–111, 2016.

[17] T. Kolobow, L. Gattinoni, and T. A. J. E. Tomlinson and Pierce, "Control of breathing using an extracorporeal membrane lung," *Anesthesiology*, vol. 46, no. 2, pp. 138–141, 1977.

[18] T. Langer, V. Vecchi, S. M. Belenkiy et al., "Extracorporeal gas exchange and spontaneous breathing for the treatment of acute respiratory distress syndrome: an alternative to mechanical ventilation?" *Critical Care Medicine*, vol. 42, no. 3, pp. e211–e220, 2014.

[19] T. Mauri, G. Grasselli, G. Suriano et al., "Control of respiratory drive and effort in extracorporeal membrane oxygenation patients recovering from severe acute respiratory distress syndrome," *Anesthesiology*, vol. 125, no. 1, pp. 159–167, 2016.

[20] J. Shen, W. Yu, J. Shi et al., "Effect of venovenous extracorporeal membrane oxygenation on the heart in a healthy piglet model," *Journal of Cardiothoracic Surgery*, vol. 8, no. 1, article 163, 2013.

[21] J. Golej, H. Kahlbacher, G. Schöffmann et al., "The immediate haemodynamic response to the initiation of extracorporeal membrane oxygenation in a piglet model of infant hypoxic respiratory failure," *Perfusion*, vol. 17, no. 6, pp. 421–426, 2002.

[22] T. Aokage, K. Palmér, S. Ichiba, and S. Takeda, "Extracorporeal membrane oxygenation for acute respiratory distress syndrome," *Journal of Intensive Care*, vol. 3, no. 1, article 17, 2015.

[23] P. L. Bosarge, L. A. Raff, G. McGwin et al., "Early initiation of extracorporeal membrane oxygenation improves survival in adult trauma patients with severe adult respiratory distress syndrome," *Journal of Trauma and Acute Care Surgery*, vol. 81, no. 2, pp. 236–243, 2016.

[24] G. J. Peek, M. Mugford, R. Tiruvoipati et al., "Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial," *The Lancet*, vol. 374, no. 9698, pp. 1351–1363, 2009.

[25] N. Patroniti, A. Zangrillo, F. Pappalardo et al., "The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks," *Intensive Care Medicine*, vol. 37, no. 9, pp. 1447–1457, 2011.

[26] H. D. Kanji, J. McCallum, M. Norena et al., "Early veno-venous extracorporeal membrane oxygenation is associated with lower mortality in patients who have severe hypoxemic respiratory failure: A retrospective multicenter cohort study," *Journal of Critical Care*, vol. 33, pp. 169–173, 2016.

[27] S. Grasso, P. Terragni, A. Birocco et al., "ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure," *Intensive Care Medicine*, vol. 38, no. 3, pp. 395–403, 2012.

[28] Y. Cheng, M. Wu, Y. Chang, C. Huang, and P. Lin, "Developing a simple preinterventional score to predict hospital mortality in adult venovenous extracorporeal membrane oxygenation: a pilot study," *Medicine*, vol. 95, no. 30, Article ID e4380, 2016.

[29] C.-H. Hsin, M.-Y. Wu, C.-C. Huang, K.-C. Kao, and P.-J. Lin, "Venovenous extracorporeal membrane oxygenation in adult respiratory failure: scores for mortality prediction," *Medicine*, vol. 95, no. 25, Article ID e3989, 2016.

[30] X. Liu, Y. Xu, R. Zhang et al., "Survival Predictors for Severe ARDS Patients Treated with Extracorporeal Membrane Oxygenation: A Retrospective Study in China," *PLOS ONE*, vol. 11, no. 6, Article ID e0158061, 2016.

[31] M. Li, L. Yi, X. Huang et al., "Factors affecting the outcome of pulmonary-acute respiratory distress syndrome patients

treated with veno-venous extracorporeal membrane oxygenation," *Zhonghua Yi Xue Za Zhi*, vol. 96, no. 10, pp. 781–786, 2016.

[32] J. H. Song, W. K. Woo, S. H. Song et al., "Outcome of veno-venous extracorporeal membrane oxygenation use in acute respiratory distress syndrome after cardiac surgery with cardiopulmonary bypass," *Journal of Thoracic Disease*, vol. 8, no. 7, pp. 1804–1813, 2016.

[33] G. F. Nieman, J. Satalin, P. Andrews, N. M. Habashi, and L. A. Gatto, "Lung stress, strain, and energy load: engineering concepts to understand the mechanism of ventilator-induced lung injury (VILI)," *Intensive Care Medicine Experimental*, vol. 4, article no. 16, 2016.

[34] D. Dreyfuss, P. Soler, G. Basset, and G. Saumon, "High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure," *American Review of Respiratory Disease*, vol. 137, no. 5, pp. 1159–1164, 1988.

[35] G. F. Curley, J. G. Laffey, H. Zhang, and A. S. Slutsky, "Biotrauma and ventilator-induced lung injury: clinical implications," *Chest*, vol. 150, no. 5, pp. 1109–1117, 2016.

[36] Z. Zhang, X. Hu, X. Zhang et al., "Lung protective ventilation in patients undergoing major surgery: a systematic review incorporating a Bayesian approach," *BMJ Open*, vol. 5, no. 9, Article ID e007473, 2015.

[37] W.-J. Gu, F. Wang, and J.-C. Liu, "Effect of lung-protective ventilation with lower tidal volumes on clinical outcomes among patients undergoing surgery: a meta-analysis of randomized controlled trials," *CMAJ*, vol. 187, no. 3, pp. E101–E109, 2015.

[38] M. B. P. Amato, C. S. V. Barbas, D. M. Medeiros et al., "Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome," *New England Journal of Medicine*, vol. 338, no. 6, pp. 347–354, 1998.

[39] C. Wang, X. Wang, C. Chi et al., "Lung ventilation strategies for acute respiratory distress syndrome: a systematic review and network meta-analysis," *Scientific Reports*, vol. 6, Article ID 22855, 2016.

[40] R. G. Brower, C. B. Shanholtz, H. E. Fessler et al., "Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients," *Critical Care Medicine*, vol. 27, no. 8, pp. 1492–1498, 1999.

[41] L. Brochard, F. Roudot-Thoraval, E. Roupie et al., "Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 158, no. 6, pp. 1831–1838, 1998.

[42] Network TARDS, "Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network," *The New England Journal of Medicine*, vol. 342, no. 18, pp. 1301–1308, 2000.

[43] M. Schmidt, C. Stewart, M. Bailey et al., "Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study," *Critical Care Medicine*, vol. 43, no. 3, pp. 654–664, 2015.

[44] A. Güldner, T. Kiss, T. Bluth et al., "Effects of ultraprotective ventilation, extracorporeal carbon dioxide removal, and spontaneous breathing on lung morphofunction and inflammation in experimental severe acute respiratory distress syndrome," *Anesthesiology*, vol. 122, no. 3, pp. 631–646, 2015.

[45] V. M. Ranieri, P. P. Terragni, L. Del Sorbo et al., "Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal," *Anesthesiology*, vol. 111, no. 4, pp. 826–835, 2009.

[46] J. D. Marhong, T. Telesnicki, L. Munshi, L. Del Sorbo, M. Detsky, and E. Fan, "Mechanical ventilation during extracorporeal membrane oxygenation. An international survey," *Annals of the American Thoracic Society*, vol. 11, no. 6, pp. 956–961, 2014.

[47] E. Fan, L. Gattinoni, A. Combes et al., "Venovenous extracorporeal membrane oxygenation for acute respiratory failure: a clinical review from an international group of experts," *Intensive Care Medicine*, vol. 42, no. 5, pp. 712–724, 2016.

[48] A. M. Modrykamien, O. O. Hernandez, Y. Im et al., "Mechanical ventilation in patients with the acute respiratory distress syndrome and treated with extracorporeal membrane oxygenation," *ASAIO Journal*, vol. 62, no. 5, pp. 607–612, 2016.

[49] T. Pham, A. Combes, H. Roze et al., "Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis," *American Journal of Respiratory and Critical Care Medicine*, vol. 187, no. 3, pp. 276–282, 2013.

[50] V. Fanelli, M. V. Ranieri, J. Mancebo et al., "Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress sindrome," *Critical Care*, vol. 20, no. 1, article 36, 2016.

[51] L. Gattinoni, A. Pesenti, D. Mascheroni et al., "Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure," *Journal of the American Medical Association*, vol. 256, no. 7, pp. 881–886, 1986.

[52] R. L. Chatburn and E. Mireles-Cabodevila, "Closed-loop control of mechanical ventilation: description and classification of targeting schemes," *Respiratory Care*, vol. 56, no. 1, pp. 85–102, 2011.

[53] J.-M. Arnal, A. Garnero, D. Novonti et al., "Feasibility study on full closed-loop control ventilation (IntelliVent-ASV™) in ICU patients with acute respiratory failure: a prospective observational comparative study," *Critical Care*, vol. 17, no. 5, article R196, 2013.

[54] J.-M. Arnal, M. Wysocki, C. Nafati et al., "Automatic selection of breathing pattern using adaptive support ventilation," *Intensive Care Medicine*, vol. 34, no. 1, pp. 75–81, 2008.

[55] N. Clavieras, M. Wysocki, Y. Coisel et al., "Prospective randomized crossover study of a new closed-loop control system versus pressure support during weaning from mechanical ventilation," *Anesthesiology*, vol. 119, no. 3, pp. 631–641, 2013.

[56] C. Karagiannidis, M. Lubnow, A. Philipp et al., "Autoregulation of ventilation with neurally adjusted ventilatory assist on extracorporeal lung support," *Intensive Care Medicine*, vol. 36, no. 12, pp. 2038–2044, 2010.

[57] S. Grasso, P. Terragni, L. Mascia et al., "Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury," *Critical Care Medicine*, vol. 32, no. 4, pp. 1018–1027, 2004.

[58] S. Grasso, T. Stripoli, M. De Michele et al., "ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure," *American Journal of Respiratory and Critical Care Medicine*, vol. 176, no. 8, pp. 761–767, 2007.

[59] D. Talmor, T. Sarge, A. Malhotra et al., "Mechanical ventilation guided by esophageal pressure in acute lung injury," *New England Journal of Medicine*, vol. 359, no. 20, pp. 2095–2104, 2008.

[60] M. O. Meade, D. J. Cook, G. H. Guyatt et al., "Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial," *JAMA*, vol. 299, no. 6, pp. 637–645, 2008.

[61] S. Y. Park, H. J. Kim, K. H. Yoo et al., "The efficacy and safety of prone positioning in adults patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials," *Journal of Thoracic Disease*, vol. 7, no. 3, pp. 356–367, 2015.

[62] L. G. Gattinoni, G. Tognoni, A. Pesenti et al., "Effect of prone positioning on the survival of patients with acute respiratory failure," *New England Journal of Medicine*, vol. 345, no. 8, pp. 568–573, 2001.

[63] C. Guérin, S. Gaillard, S. Lemasson et al., "Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial," *The Journal of the American Medical Association*, vol. 292, no. 19, pp. 2379–2387, 2004.

[64] C. Guérin, J. Reignier, J.-C. Richard et al., "Prone positioning in severe acute respiratory distress syndrome," *New England Journal of Medicine*, vol. 368, no. 23, pp. 2159–2168, 2013.

[65] A. Kimmoun, S. Roche, C. Bridey et al., "Prolonged prone positioning under VV-ECMO is safe and improves oxygenation and respiratory compliance," *Annals of Intensive Care*, vol. 5, no. 1, article 35, 2015.

[66] V. Kipping, S. Weber-Carstens, C. Lojewski et al., "Prone position during ECMO is safe and improves oxygenation," *International Journal of Artificial Organs*, vol. 36, no. 11, pp. 821–832, 2013.

[67] J. Litmathe, C. Sucker, J. Easo, L. Wigger, and O. Dapunt, "Prone and ECMO—a contradiction per se?" *Perfusion*, vol. 27, no. 1, pp. 78–82, 2012.

[68] Y. Masuda, H. Tatsumi, H. Imaizumi et al., "Effect of prone positioning on cannula function and impaired oxygenation during extracorporeal circulation," *Journal of Artificial Organs*, vol. 17, no. 1, pp. 106–109, 2014.

[69] M. Kredel, L. Bischof, T. E. Wurmb, N. Roewer, and R. M. Muellenbach, "Combination of positioning therapy and venovenous extracorporeal membrane oxygenation in ARDS patients," *Perfusion*, vol. 29, no. 2, pp. 171–177, 2014.

[70] C. Guervilly, S. Hraiech, V. Gariboldi et al., "Prone positioning during veno-venous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome in adults," *Minerva Anestesiologica*, vol. 80, no. 3, pp. 307–313, 2014.

[71] J. Mancebo, R. Fernández, L. Blanch et al., "A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 173, no. 11, pp. 1233–1239, 2006.

[72] R. E. Culbreth and L. T. Goodfellow, "Complications of prone positioning during extracorporeal membrane oxygenation for respiratory failure: a systematic review," *Respiratory Care*, vol. 61, no. 2, pp. 249–254, 2016.

[73] L. C. Otterspoor, F. H. Smit, T. J. Van Laar, J. Kesecioglu, and D. Van Dijk, "Prolonged use of extracorporeal membrane oxygenation combined with prone positioning in patients with acute respiratory distress syndrome and invasive Aspergillosis," *Perfusion*, vol. 27, no. 4, pp. 335–337, 2012.

[74] M. T. Voelker, N. Jahn, S. Bercker et al., "Prone positioning of patients during venovenous extracorporeal membrane oxygenation is safe and feasible," *Der Anaesthesist*, vol. 65, no. 4, pp. 250–257, 2016.

[75] C. E. Goettler, J. P. Pryor, B. A. Hoey, J. K. Phillips, M. C. Balas, and M. B. Shapiro, "Prone positioning does not affect cannula function during extracorporeal membrane oxygenation or continuous renal replacement therapy," *Critical Care*, vol. 6, no. 5, pp. 452–455, 2002.

[76] A. Güldner, P. Pelosi, and M. G. De Abreu, "Spontaneous breathing in mild and moderate versus severe acute respiratory distress syndrome," *Current Opinion in Critical Care*, vol. 20, no. 1, pp. 69–76, 2014.

[77] L. Papazian, J.-M. Forel, A. Gacouin et al., "Neuromuscular blockers in early acute respiratory distress syndrome," *The New England Journal of Medicine*, vol. 363, no. 12, pp. 1107–1116, 2010.

[78] G. Lyu, X. Wang, W. Jiang, T. Cai, and Y. Zhang, "[Clinical study of early use of neuromuscular blocking agents in patients with severe sepsis and acute respiratory distress syndrome]," *Zhonghua wei zhong bing ji jiu yi xue*, vol. 26, no. 5, pp. 325–329, 2014.

[79] A. S. Neto, V. G. M. Pereira, D. C. Espósito, M. C. T. Damasceno, and M. J. Schultz, "Neuromuscular blocking agents in patients with acute respiratory distress syndrome: a summary of the current evidence from three randomized controlled trials," *Annals of Intensive Care*, vol. 2, no. 1, article 33, 2012.

[80] M. Gainnier, A. Roch, J.-M. Forel et al., "Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome," *Critical Care Medicine*, vol. 32, no. 1, pp. 113–119, 2004.

[81] J.-M. Forel, A. Roch, V. Marin et al., "Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome," *Critical Care Medicine*, vol. 34, no. 11, pp. 2749–2757, 2006.

[82] A.-T. Wang, J.-L. Gao, X.-L. Li, Y.-X. Leng, Z.-Y. Yao, and X. Zhu, "The effect of neuromuscular blocking agents on prognosis of patients with acute respiratory distress syndrome: a meta analysis," *Chinese Critical Care Medicine*, vol. 25, no. 3, pp. 149–153, 2013.

[83] T. Langer, A. Santini, N. Bottino et al., "'Awake' extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering," *Critical Care*, vol. 20, no. 1, article 150, 2016.

[84] M. A. Schechter, A. M. Ganapathi, B. R. Englum et al., "Spontaneously Breathing Extracorporeal Membrane Oxygenation Support Provides the Optimal Bridge to Lung Transplantation," *Transplantation*, vol. 100, no. 12, pp. 2699–2704, 2016.

[85] H. J. Yeo, W. H. Cho, and D. Kim, "Awake extracorporeal membrane oxygenation in patients with severe postoperative acute respiratory distress syndrome," *Journal of Thoracic Disease*, vol. 8, no. 1, pp. 37–42, 2016.

[86] R. Marcolin, D. Mascheroni, A. Pesenti, M. Bombino, and L. Gattinoni, "Ventilatory impact of partial extracorporeal CO2 removal (PECOR) in ARF patients," *ASAIO transactions*, vol. 32, no. 1, pp. 508–510, 1986.

[87] S. K. Powers, A. N. Kavazis, and S. Levine, "Prolonged mechanical ventilation alters diaphragmatic structure and function," *Critical Care Medicine*, vol. 37, no. 10, pp. S347–S353, 2009.

[88] S. Levine, T. Nguyen, N. Taylor et al., "Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans," *The New England Journal of Medicine*, vol. 358, no. 13, pp. 1327–1335, 2008.

[89] R. Hering, J. C. Bolten, S. Kreyer et al., "Spontaneous breathing during airway pressure release ventilation in experimental lung injury: effects on hepatic blood flow," *Intensive Care Medicine*, vol. 34, no. 3, pp. 523–527, 2008.

[90] D. Abrams, J. Javidfar, E. Farrand et al., "Early mobilization of patients receiving extracorporeal membrane oxygenation: A

Retrospective Cohort Study," *Critical Care*, vol. 18, no. 1, article R38, 2014.

[91] T. Fuehner, C. Kuehn, J. Hadem et al., "Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation," *American Journal of Respiratory and Critical Care Medicine*, vol. 185, no. 7, pp. 763–768, 2012.

[92] K. E. Williams, "Extracorporeal membrane oxygenation for acute respiratory distress syndrome in adults," *AACN Advanced Critical Care*, vol. 24, no. 2, pp. 149–158, 2013.

Hindawi Publishing Corporation
Canadian Respiratory Journal
Volume 2016, Article ID 3257846, 5 pages
http://dx.doi.org/10.1155/2016/3257846

Research Article

Factors Associated with ICU Admission following Blunt Chest Trauma

Andrea Bellone,[1] Ilaria Bossi,[2] Massimiliano Etteri,[2] Francesca Cantaluppi,[2] Paolo Pina,[2] Massimo Guanziroli,[2] AnnaMaria Bianchi,[2] and Giovanni Casazza[3]

[1]*Emergency Ward, Niguarda Hospital, Milan, Piazza Ospedale Maggiore 3, 20162 Milano, Italy*
[2]*Emergency Ward, Azienda Ospedaliera Sant'Anna di Como, Via Ravona 19, 22020 Como, Italy*
[3]*Dipartimento di Scienze Biomediche e Cliniche L. Sacco, Università degli Studi di Milano, Via GB Grassi 74, 20157 Milano, Italy*

Correspondence should be addressed to Andrea Bellone; andrea.bellone@ospedaleniguarda.it

Received 31 August 2016; Revised 10 October 2016; Accepted 27 October 2016

Academic Editor: Zhongheng Zhang

Background. Blunt chest wall trauma accounts for over 10% of all trauma patients presenting to emergency departments worldwide. When the injury is not as severe, deciding which blunt chest wall trauma patients require a higher level of clinical input can be difficult. We hypothesized that patient factors, injury patterns, analgesia, postural condition, and positive airway pressure influence outcomes. *Methods*. The study population consisted of patients hospitalized with at least 3 rib fractures (RF) and at least one pulmonary contusion and/or at least one pneumothorax lower than 2 cm. *Results*. A total of 140 patients were retrospectively analyzed. Ten patients (7.1%) were admitted to intensive care unit (ICU) within the first 72 hours, because of deterioration of the clinical conditions and gas exchange with worsening of chest X-ray/thoracic ultrasound/chest computed tomography. On univariable analysis and multivariable analysis, obliged orthopnea ($p = 0.0018$) and the severity of trauma score ($p < 0.0002$) were associated with admission to ICU. *Conclusions*. Obliged orthopnea was an independent predictor of ICU admission among patients incurring non-life-threatening blunt chest wall trauma. The main therapeutic approach associated with improved outcome is the prevention of pulmonary infections due to reduced tidal volume, namely, upright postural condition and positive airway pressure.

1. Introduction

Blunt chest wall trauma accounts for over 10% of all trauma patients presenting to emergency departments worldwide [1]. Research has highlighted significant morbidity and mortality for the blunt chest wall trauma patient, with reported mortality ranging from 4 to 20% [1, 2]. The patient with severe thoracic injuries will be managed in the emergency department (Dpt) by trauma and various surgical teams and intervention is dictated by the resuscitation protocol of the department [3]. Disposition of chest injury patients from the emergency department is therefore straightforward when the patient requires immediate surgery or supportive mechanical ventilation [3]. When the injury is not as severe or associate injuries are not present or are minor, deciding which blunt chest wall trauma patients require a higher level of clinical input can be difficult. Clinical symptoms are not considered an accurate predictor of outcome following non-life-threatening blunt chest wall trauma [4]. The aim of this study was to identify the risk factors for admission to the intensive care unit in non-life-threatening patients with blunt chest trauma admitted to the emergency medicine ward and immediately submitted to a strategy that included positive airway pressure, upright position, and pain-control by pharmacologic therapy.

2. Materials and Methods

2.1. Participants and Study Design. This study was performed in a busy, level 1 trauma center. Between January 2013 and December 2014, 140 patients with non-life-threatening blunt chest wall trauma were reviewed retrospectively. Approval

was obtained from the institutional review board. All injured patients received a standardized examination including bedside chest and pelvis radiography, abdominal and thoracic ultrasound (extended focused assessment with sonography for trauma), and computed tomography of head, spine, chest, abdomen, and pelvis. As a part of the routine, plain radiography of the chest was taken 48 hours after admission in the emergency ward.

Patients were enrolled in the study according to the criteria listed as follows.

Inclusion Criteria. They include the following: (1) 18 years of age or more; (2) more than three rib fractures and/or lung contusion and/or pneumothorax and/or sternal fracture; (3) admission to the hospital within 24 hours after injury.

Exclusion Criteria. They include the following: (1) chest wall trauma score more than 7 [5]; (2) pressure of arterial oxygen/fractional inspired oxygen concentration (PaO_2/FiO_2) < 250; (3) the need for vasopressor agents; (4) the need for immediate intubation and mechanical ventilation; (5) the need for pneumothorax drainage; (6) severe traumatic injury other than blunt chest wall trauma.

All patients were submitted to a standardized therapeutic program: (1) keeping the posture at 45° or more; (2) cycle of positive airway pressure by Continuous Positive Airway Pressure (CPAP) trial (three hours every six hours) for the first 24 hours: in the next period, patients were encouraged to blow through a tube with 10 cm of water for at least 5 minutes every three hours; (3) patient-controlled analgesia by 200 mg of tapentadol a day; if not effective as reported by numerical rating scale (NRS) more than 7, we used transcutaneous fentanyl (50 mcg/hour) as rescue therapy.

The aim of our study was to identify the risk factors for the admission to the ICU. The decision to admit patients to the ICU was made by the senior emergency, surgical, and intensive care/anaesthetic doctor. We used as criteria for improving our decision the following: PaO_2/FiO_2 < 250; the need for vasopressor agents; and the need for immediate intubation and mechanical ventilation.

2.2. Statistical Analysis. Descriptive analyses were performed by calculating mean (±standard deviation, SD) or median (interquartile range, IQR), as appropriate, for quantitative continuous variables. Categorical variables were reported as count (percentage).

Univariate and multivariate logistic regression analyses were performed [6] to assess the effect of age (dichotomized, >65 years versus ≤65 years), chest wall score, injury score, SpO_2, number of ribs fractures, chest contusion, and obliged orthopnea on the risk of being admitted to the ICU. Only those variables that were statistically significant in univariate models were considered in multivariate analysis.

Results were reported as odds ratios (OR) with 95% confidence intervals (CI).

The *c*-statistic, ranging from 0.5 (chance prediction) to 1.0 (perfect prediction of the events), was used to assess the predictive ability of the logistic models.

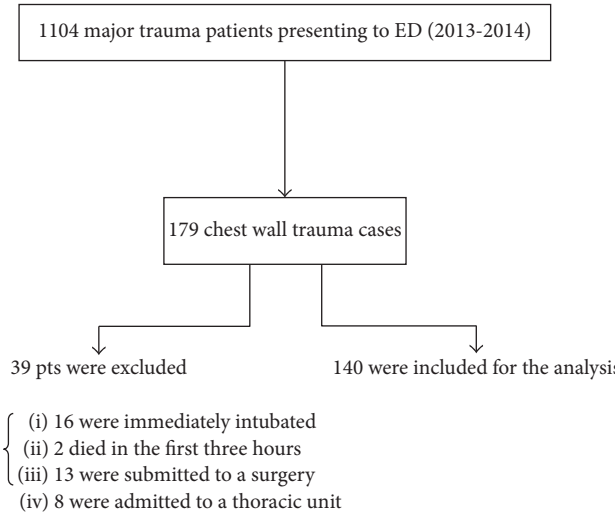


Figure 1: Flow diagram.

p values less than 0.05, two-tailed, were considered statistically significant. All of the statistical analyses were performed using SAS statistical software (release 9.4, SAS Institute Inc., Cary, NC, USA).

3. Results

During the study period, 1104 consecutive patients were admitted to our hospital because of major trauma. Of these, 179 patients presented mainly chest wall trauma. Thirty-nine patients were excluded from the study (16 patients were immediately intubated, two patients died in the first three hours, 13 patients were sent to the operating surgery, and 8 patients were admitted to the thoracic unit) (Figure 1). One hundred forty met the inclusion criteria for our study. Of all included patients 80% were victims of high energy chest trauma, due to car or motorcycle crashes or falls from large height, while the 20% were victims of low energy trauma with minor car crashes or domestic accidents.

All patients were submitted to patient-controlled analgesia, upright postural condition, and positive airway pressure in Dpt of emergency (Table 1). Only 11 patients had to prolong CPAP treatment for 36 hours because of the respiratory distress persistence.

Ten of these patients (7.1%) went on to require ICU admission within the first 72 hours, because of a deterioration of the clinical conditions and gas exchange. For all patients were performed chest US and chest XR and in 7 cases they showed an enlargement of pulmonary consolidations confirmed with CT scan.

The characters of these patients in terms of trauma severity were not significantly different compared with the remaining patients (Table 3). None of these patients died.

The 130 patients were discharged from the emergency ward and the medium length of stay in hospital was 6.4 days. No patients were admitted to our hospital in the next two months.

The mean injury severity score was 15 [7]. The mean chest wall score was 4, 7 [8]. The median number of fractured ribs

Table 1: Characteristics of patients on admission.

Age (years)	Mean (range)	66 (52–76)
Sex	F	41 (29.3%)
	M	99 (70.7%)
Charlson comorbidity index	0–3	81 (57,8%)
	>3	59 (42.2%)
SpO_2	Mean (range)	96% (94%–98%)
Number of ribs fractures	0–3	63 (45%)
	>3	77 (55%)
PNX	Yes	48 (34.3%)
	No	92 (65.7%)
Number of chest contusions	0	103 (73.6%)
	1	23 (16.4%)
	≥2	14 (10.0%)
Head injury	Yes	39 (27.9%)
	No	101 (72.1%)
Hipbone	Yes	4 (2.9%)
	No	136 (97.1%)
Spine fracture	Yes	21 (15.0%)
	No	119 (85.5%)
Previous anticoagulant therapy	Yes	11 (7.9%)
	No	129 (92.1%)
Clavicula/sterna/scapula fractures	Yes	38 (27.1%)
	No	102 (72.9%)

was 4 (IQR 3–6). Oxygenation as measured by arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) and respiratory function as measured by respiratory rate, serum pH, pCO_2, and bicarbonate before the initial management are presented in Table 2.

Tapentadol was used in 89% of patients. Only 11% of patients needed transcutaneous fentanyl because of numeric rating scale (NRS) more than 7.

At univariate analysis, the injury score and obliged orthopnea were the only statistically significant factors for the prediction of the admission to the ICU (Table 2). This result was confirmed in the multivariate analysis (injury score, OR = 1.17, 95% CI 1.06 to 1.30, and $p = 0.0018$; obliged orthopnea OR = 20.3, 95% CI 4.08 to 101.4, and $p = 0.0002$). The multivariate model containing the injury score and obliged orthopnea showed an overall good predictive ability (c-statistic = 0.914).

Following multivariate analysis, the obliged postural condition was a significant factor associated with ICU requirement.

4. Discussion

As no current guidelines exist for the management of this patient group, recognition of the high risk patient in the ED is not always straightforward due to the nature of the injury and its recovery phase. The blunt chest wall trauma patient who can walk into the ED with no immediate life-threatening injury will commonly develop complications up to 72 h or more after injury, which may also prove life-threatening [9, 10]. An understanding of the risk factors for development of late complications in blunt chest wall trauma patient requiring the admission to the ICU could assist in the accurate risk stratification of this patient group in the ED and thus improve outcomes.

Our study has three strengths: our approach was aggressive. We start pain management with pharmacologic therapy. Our decision was in favour of the pharmacological pain-control because two previous studies showed that the insertion of intercostal catheters was significantly associated with morbidity [10, 11]; secondly, all patients were immediately submitted to a positive airway pressure by mask or by a tube. It is well known that, in chest trauma, a lung lesion such as pulmonary contusion or pneumothorax and/or thoracic injury can promote systemic inflammatory activation and consequently an acute respiratory failure due to alveolar collapse and impaired fluid clearance [12]. Recently a systematic review and meta-analysis suggested that noninvasive ventilation could be useful in the management of acute respiratory failure due to chest trauma [13]; third, to keep an obliged posture at, at least, 45 degrees means to improve the ventilation/perfusion ratio by increasing the functional residual capacity with a better ventilation distribution towards more perfused lung areas [14].

A previous study that analyzed factors associated with survival following blunt chest trauma in older patients showed that age and injury severity score were independent predictors of survival [15]. On the opposite, another study showed that the risk factors for the development of complications in the recovery phase following blunt chest wall trauma were a patient age of 65 years or more, three or more rib fractures, chronic lung disease or cardiovascular disease, the use of preinjury anticoagulants, and oxygen saturation level in the ED of less than 90% [16].

In our study, two factors were associated with patients' admission to the ICU from the emergency ward. Patients with high injury score and patients with obliged orthopnea were at high risk of admission to the ICU. These two factors showed an excellent ability in predicting admission to the ICU, as shown by the high value of the c-statistic (0.91).

In particular data regarding obliged orthopnea testify that the topics of chest trauma management should be based on three principles (pain-control, positive airway pressure, and posture) serving all together to prevent atelectasis and lung infection. Age, oxygenation, number of rib fractures, comorbidity, and preinjury anticoagulants do not seem to affect patients' outcome in non-life-threatening blunt chest wall trauma. Data should be confirmed with larger and different clinical records.

This study has limitations. Retrospective data were used. Such analyses are prone to selection bias and, in general, are more suitable for developing study questions rather than answering scientific questions. Secondly, the analysis of patients was performed in only one center. Third, the number of studied patients is limited. Since we observed only

Table 2: Statistical analysis.

Variable	Univariate model		Multivariate model	
Age > 65 yrs	1.25 (0.38 to 4.07)	0.7162	—	
Chest wall score	1.10 (0.72 to 1.67)	0.6648	—	
Injury score	1.16 (1.07 to 1.25)	0.0002	1.17 (1.06 to 1.30)	0.0018
SpO_2	0.90 (0.80 to 1.01)	0.0818	—	
Number of ribs fractures	1.18 (0.96 to 1.46)	0.1230	—	
Chest contusion	2.14 (0.64 to 7.23)	0.2190	—	
Fractures with immobilization	22.6 (5.50 to 92.9)	<0.0001	20.3 (4.08 to 101.4)	0.0002

c-statistic for multivariate model: 0.914.

Table 3: Patients admitted to ICU.

Age (years)	Mean (range)	71 (58–76)
Sex	F	5 (50%)
	M	5 (50%)
Charlson comorbidity index	0–3	8 (80%)
	>3	2 (20%)
SpO_2		93,8% (75%–100%)
Number ribs fractures	0–3	3 (30%)
	>3	7 (70%)
PNX	Yes	6 (60%)
	No	4 (40%)
Number chest contusions	0	4 (40%)
	1	1 (10%)
	≥2	5 (50%)
Head injury	Yes	3 (30%)
	No	7 (70%)
Hipbone fracture	Yes	2 (20%)
	No	8 (80%)
Spine fracture	Yes	3 (30%)
	No	7 (70%)
Previous anticoagulant therapy	Yes	1 (10%)
	No	9 (90%)
Clavicula/sternal/scapula fractures	Yes	2 (20%)
	No	8 (80%)
Fracture with immobilization	yes	8 (80%)
	No	2 (20%)

ten events, the results obtained with our multivariate model might be unstable. A larger multicenter study is needed to confirm our results.

Disclosure

The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Competing Interests

The authors have reported that no potential conflict of interests exists with any companies/organizations whose products or services may be discussed in this article.

Authors' Contributions

Andrea Bellone, Ilaria Bossi, and Massimiliano Etteri are the guarantors of the content of the manuscript including the data and analysis. Francesca Cantaluppi, Paolo Pina, Massimo Guanziroli, AnnaMaria Bianchi, and Giovanni Casazza contributed to the study design data collection and data analysis and approved the final version of the manuscript.

References

[1] D. W. Ziegler and N. N. Agarwal, "The morbidity and mortality of RIB fractures," *Journal of Trauma*, vol. 37, no. 6, pp. 975–979, 1994.

[2] K. A. Quaday, "Morbidity and mortality of rib fracture," *Journal of Trauma*, vol. 39, no. 3, p. 617, 1995.

[3] G. E. Blecher, B. Mitra, P. A. Cameron, and M. Fitzgerald, "Failed emergency department disposition to the ward of patients with thoracic injury," *Injury*, vol. 39, no. 5, pp. 586–591, 2008.

[4] I. Dubinsky and A. Low, "Non-life-threatening blunt chest trauma: appropriate investigation and treatment," *The American Journal of Emergency Medicine*, vol. 15, no. 3, pp. 240–243, 1997.

[5] B. Baker Sponeill, W. Haddon, and W. B. Long, "The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care," *The Journal of Trauma*, vol. 14, no. 3, pp. 187–196, 1974.

[6] Z. Zhang, "Univariate description and bivariate statistical inference: the first step delving into data," *Annals of Translational Medicine*, vol. 4, no. 5, p. 91, 2016.

[7] C. M. Pressley, W. R. Fry, A. S. Philp, S. D. Berry, and R. S. Smith, "Predicting outcome of patients with chest wall injury," *American Journal of Surgery*, vol. 204, no. 6, pp. 910–914, 2012.

[8] J. Q. Alexander, C. J. Gutierrez, M. C. Mariano et al., "Blunt chest trauma in the elderly patient: how cardiopulmonary disease affects outcome," *The American Surgeon*, vol. 66, no. 9, pp. 854–857, 2000.

[9] B. J. Simon, Q. Chu, T. A. Emhoff, V. M. Fiallo, and K. F. Lee, "Delayed hemothorax after blunt thoracic trauma: an uncommon entity with significant morbidity," *Journal of Trauma—Injury, Infection and Critical Care*, vol. 45, no. 4, pp. 673–676, 1998.

[10] M. Deneuville, "Morbidity of percutaneous tube thoracostomy in trauma patients," *European Journal of Cardio-Thoracic Surgery*, vol. 22, no. 5, pp. 673–678, 2002.

[11] S. W. Etoch, M. F. Bar-Natan, F. B. Miller et al., "Tube thoracostomy: factors related to complications," *Archives of Surgery*, vol. 130, no. 5, pp. 521–526, 1995.

[12] P. J. Papadakos, M. Karcz, and B. Lachmann, "Mechanical ventilation in trauma," *Current Opinion in Anaesthesiology*, vol. 23, no. 2, pp. 228–232, 2010.

[13] D. Chiumello, S. Coppola, S. Froio, C. Gregoretti, and D. Consonni, "Noninvasive ventilation in chest trauma: systematic review and meta-analysis," *Intensive Care Medicine*, vol. 39, no. 7, pp. 1171–1180, 2013.

[14] J. Milic-Emili, J. A. Henderson, M. B. Dolovich, D. Trop, and K. Kaneko, "Regional distribution of inspired gas in the lung," *Journal of Applied Physiology*, vol. 21, no. 3, pp. 749–759, 1966.

[15] D. T. Harrington, B. Phillips, J. Machan et al., "Factors associated with survival following blunt chest trauma in older patients: results from a large regional trauma cooperative," *Archives of Surgery*, vol. 145, no. 5, pp. 432–437, 2010.

[16] C. E. Battle, H. Hutchings, K. James, and P. A. Evans, "The risk factors for the development of complications during the recovery phase following blunt chest wall trauma: a retrospective study," *Injury*, vol. 44, no. 9, pp. 1171–1176, 2013.

Hindawi Publishing Corporation
Canadian Respiratory Journal
Volume 2016, Article ID 9092871, 8 pages
http://dx.doi.org/10.1155/2016/9092871

Review Article

Noninvasive Ventilation with Heliox for Respiratory Distress Syndrome in Preterm Infant: A Systematic Review and Meta-Analysis

Chen Long,[1] Wang Li,[1] Li Wanwei,[2] Li Jie,[3] and Shi Yuan[1]

[1]*Department of Pediatrics, Daping Hospital, Research Institute of Surgery, Third Military Medical University, Chongqing 400042, China*
[2]*Department of Blood Transfusion, Daping Hospital, Research Institute of Surgery, Third Military Medical University, Chongqing 400042, China*
[3]*Department of Obstetrics and Gynecology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400014, China*

Correspondence should be addressed to Shi Yuan; petshi530@vip.163.com

Received 11 June 2016; Revised 4 September 2016; Accepted 30 October 2016

Academic Editor: Zhongheng Zhang

Objectives. To assess whether noninvasive ventilation with Heliox reduces the need for endotracheal ventilation and subsequent complications in preterm infants with respiratory distress syndrome (RDS). *Methods.* A search of major electronic databases, including MEDLINE and the Cochrane Central Register of Controlled Trials, for randomized or quasi-randomized controlled trials that compared noninvasive ventilation with Heliox versus noninvasive ventilation with standard gas for preterm infants with RDS was performed. The primary outcome was the incidence of intubation. The secondary outcomes were the level of $PaCO_2$, the use of surfactant, and other complications. *Results.* Two randomized and one quasi-randomized controlled trials including 123 preterm infants were assessed. Heliox was found to significantly decrease the incidence of intubation (RR: 0.42; 95% CI: 0.23 to 0.78), the level of $PaCO_2$ (MD: −9.61; 95% CI: −15.76 to −03.45), and the use of surfactant (RR: 0.25; 95% CI: 0.10 to 0.61) as compared with standard gas. No significant differences were found in other secondary outcomes. *Conclusions.* Noninvasive ventilation with Heliox decreases the incidence of intubation in preterm infants suffering from RDS. However, data on clinical outcomes are limited. Larger trials are needed to verify the beneficial effects.

1. Introduction

Respiratory distress syndrome (RDS) is a condition of respiratory distress which commences at or shortly after birth and increases in severity over the first three days of life, and it also is the most common cause of morbidity and mortality in preterm infants and is related inversely to the gestational age [1]. Endotracheal ventilation and exogenous surfactant replacement therapy are two standardized therapies to reduce neonatal mortality [2]. Despite improving survival [3], endotracheal ventilation is related to increasing risks of infection and ventilation-associated lung injuries. Importantly, prolonged duration of endotracheal ventilation induces a higher probability of death or survival with neurologic impairment and/or bronchopulmonary dysplasia (BPD) in the postneonatal period [4]. There is thus a trend to minimize the use of mechanical ventilation.

To this day, early use of noninvasive respiratory support is the most effective pathway to reduce these risks above. However, noninvasive ventilation strategies are only partly helpful, as about 10.5%–50% fail and need endotracheal ventilation [5]. Since 1935, the use of Heliox (79% helium and 21% oxygen) has been proposed as a standard therapy for severe asthma, acute upper airway obstruction [6]. Helium is an inert, colorless, and odorless gas and has very low density, and when the nitrogen in inspired standard air is replaced with helium, the density of mixture is 3 times less than standard air [7]. Studies have reported beneficial effects such as the

reduction of lung inflammation, flow turbulence, and work of breathing and air-trapping and the improvement of the distal-airway transmission of aerosol particles [8], and the effects of Heliox have been attributed to the physical characteristics of helium. Recently, noninvasive ventilation strategies with Heliox have been used for the purposes of minimizing physical and chemical injuries, as well as supporting adequate gas exchange in some RCTs and non-RCTs for preterm neonates with RDS, but the clinical application was rare and the results remained inconsistent.

The objective of this systematic review was to evaluate whether noninvasive ventilation with Heliox would reduce the requirement for endotracheal ventilation and subsequent complications in preterm infants with RDS as compared with standard gas.

2. Methods

Studies were added to the review whether they were randomized or quasi-randomized controlled trials. The interventions for comparison were Heliox and standard gas in preterm infants with RDS and supported by noninvasive ventilation. We did not put restrictions on studies as to language.

The search strategies and assessment methods are similar to our previous study [5]. A systematic literature search was conducted in March 2016, using the methods of the Cochrane Collaboration for Systematic Reviews of Interventions [9]. The databases searched included MEDLINE (1980 to March 2016) and the Cochrane Central Register of Controlled Trials (all years). The keywords "nasal intermittent positive pressure ventilation (NIPPV)" or "nasal continuous positive airway pressure (CPAP)" or "bi-level positive airway pressure (BiPAP)" or "noninvasive positive pressure ventilation" and "preterm" or "premature" or "neonate" and "respiratory distress syndrome (RDS)" and "heliox" or "helium/oxygen" were used. Meantime, the search was limited to human studies. We applied the Cochrane sensitivity-maximizing and Cochrane sensitivity- and precision-maximizing strategies as our special search strategies [9]. The criteria for a trial to be included in the meta-analysis were as follows: (1) trial involving preterm infants with RDS and (2) trial comparing noninvasive ventilation with Heliox and standard gas.

The studies obtained through the search strategies described above were imported to an electronic bibliographic management program. We reviewed the titles and abstracts of the remaining articles and excluded those that were not related to our topic and those that did not meet the eligibility criteria. The full-text versions were obtained for the relevant articles that could be included in the review.

The research strategies, article-extracting, and data analysis were performed independently by three reviewers. Data analysis included study design, study interventions, number of subjects in each group, demographic characteristics, inclusion and exclusion criteria, primary and secondary outcomes, and variables used to assess study quality.

The primary outcome was the need for intubation, and the observation time was any time before discharge. The secondary outcomes were the level of $PaCO_2$ at the time Heliox ceased, the use of surfactant and subsequent complications, including the incidences of BPD, intraventricular hemorrhage (IVH) of any grade, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), and periventricular leukomalacia (PVL), total time of noninvasive ventilation, duration of hospitalization, and death before hospital discharge.

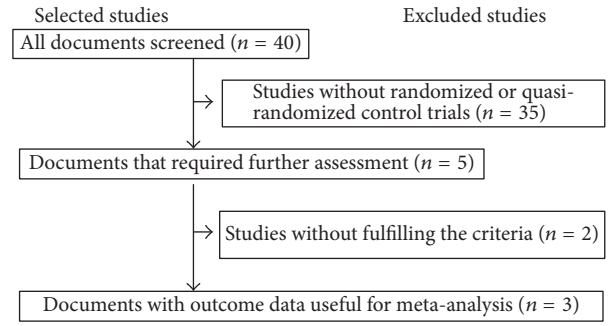


Figure 1: The selection course of the included papers.

The Cochrane Risk of Bias tool [9] was applied to assess the methodological quality of the included studies. Discrepancies between the three reviewers were resolved through discussion (Table 3). Meta-analysis was performed using version 5.2 of Review Manager. To assess heterogeneity, 2 distribution and Higgins I^2 statistics were calculated to determine the percentage of total variation across studies resulting from heterogeneity. I^2 statistics approximating 25%, 50%, and 75% were considered low, medium, and high heterogeneity, respectively. The fixed-effects models were present, and the random-effects models were used whenever considerable heterogeneity was shown. For categorical data, the effect is expressed as the RR, and for continuous data the effect is expressed as the weighted mean difference (95% CI).

3. Results

3.1. Description of Studies. Forty studies were identified, of which thirty-five were excluded because they were not RCTs or quasi-RCTs. Five trials underwent further evaluation, and two were excluded because they did not meet the inclusion criteria. Three eligible studies were included in the final analysis [10–12] (Figure 1).

Tables 1–3 summarized the characteristics and quality assessments of these studies. These studies were conducted in Italy and China. A total of 123 infants were enrolled in the three studies. Two studies were RCTs and one study was quasi-RCT.

3.2. Primary Outcomes. Each study reported the requirement for intubation and mechanical ventilation. The meta-analysis estimated a significant decrease for the need for invasive ventilation in the Heliox group as compared with the standard gas group (RR: 0.42; 95% CI: 0.23–0.78) in the fixed-effects model (Figure 2). Heterogeneity was not found among the 3 trials ($P = 0.34$, $I^2 = 8\%$).

Table 1: The characteristics of included papers.

	N (n)		Gestational age (weeks)		Birth weight (g)		Male	
	Heliox	Standard air	Heliox	Standard air	Heliox	Standard air	Heliox	Standard air
Li et al. 2014	19	17	34.2 ± 1.8	34.3 ± 1.8	2150 ± 470	2190 ± 440	13	10
Dani et al. 2013	18	18	25.4 ± 1.5	25.8 ± 1.9	680 ± 150	750 ± 190	10	7
Colnaghi et al. 2012	27	24	30.6 ± 1.4	30.6 ± 1.2	1454.0 ± 332.2	1430.3 ± 327.4	18	15

Table 2: Details of included papers.

	Li et al. 2014	Dani et al. 2013	Colnaghi et al. 2012
Single or multicenter design	Single	Single	Multicenter
Mode of noninvasive ventilation	NIPPV	NCPAP or BiPAP	NCPAP
Time of Heliox administration (hours)	3	24	12
Heliox expenditure (¥/infant)	2000	—	7500
Whether or not surfactant was given	Surfactant was given only as rescue therapy	Early rescue surfactant treatment when $FiO_2 > 0.30$	Surfactant was given only as rescue therapy
Whether or not noninvasive ventilation was used as primary support	Yes	No	Yes
Side effects	No	No	No

Exchange rate in 1/1/2008: 1¥ = 0.1€.

Table 3: Bias assessment of included papers.

	Li et al. 2014	Dani et al. 2013	Colnaghi et al. 2012
Allocation concealment	Yes	No	Yes
Sequence generation	Yes	No	Yes
Blinding (participants)	Unclear	Unclear	Unclear
Blinding (outcome assessors)	Yes	Unclear	Yes
Incomplete data address	Yes	Yes	Yes
Free of selective reporting	Yes	Yes	Yes
Free of other biases	No	Unclear	Unclear

3.3. Secondary Outcomes. Data for the secondary outcome demonstrated a significant decrease for the level of $PaCO_2$ in the Heliox group (mean difference: −9.61; 95% CI: −15.76–−3.45), with heterogeneity among the two trials ($P = 0.04$, $I^2 = 76\%$) (Figure 3).

Data also demonstrated a significant decrease for the use of surfactant in the Heliox group (RR: 0.25; 95% CI: 0.10–0.61), without heterogeneity among the two included trials ($P = 0.85$, $I^2 = 0\%$) (Figure 4).

No significant differences were found in other secondary outcomes of included studies between the two groups (Table 4).

4. Discussion

In the present meta-analysis involving three RCTs, we aimed to assess the rate of endotracheal intubation and subsequent complications in preterm infants with RDS through comparing noninvasive ventilation with Heliox and standard gas. The results showed a significant decrease for the need of endotracheal intubation in the Heliox group as compared with the standard gas group. Similarities also appeared in the clearance of $PaCO_2$ and the use of surfactant. These findings suggest that Heliox does increase the beneficial effects of noninvasive ventilation and contribute to a reduced risk of endotracheal ventilation in preterm infants with noninvasive ventilation.

Previous studies have demonstrated the beneficial effects of Heliox compared with standard gas in preterm infants. Specifically, Heliox has been shown to significantly reduce the requirement for ventilatory support and improve gas exchange [13–15]. A recent meta-analysis found that infants treated with Heliox had a significantly lower mean clinical respiratory score in the first hour after starting treatment when compared to those treated with air or oxygen [16]. And these results were consistent with the present meta-analysis. However, there were significant heterogeneities. One of the causes of heterogeneities might be the observation time of intervention. Among the trials included, the observation

Study or subgroup	Heliox Events	Heliox Total	Standard gas Events	Standard gas Total	Weight	Risk ratio M-H, fixed, 95% CI
Colnaghi et al. 2012	4	27	11	24	47.9%	0.32 [0.12, 0.88]
Dani et al. 2013	6	18	9	18	37.0%	0.67 [0.30, 1.48]
Li et al. 2014	0	19	3	17	15.1%	0.13 [0.01, 2.32]
Total (95% CI)		*64*		*59*	*100.0%*	*0.42 [0.23, 0.78]*
Total events	10		23			

Heterogeneity: $\chi^2 = 2.18$, df = 2 ($P = 0.34$); $I^2 = 8\%$

Test for overall effect: $Z = 2.77$ ($P = 0.006$)

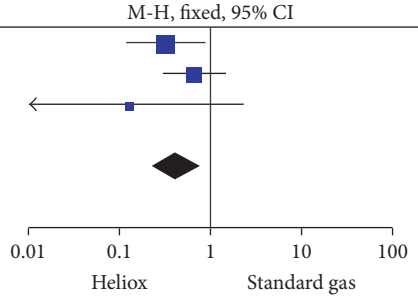


Figure 2: The comparison of Heliox versus standard air for the incidence of intubation.

Study or subgroup	Heliox Mean	Heliox SD	Heliox Total	Standard gas Mean	Standard gas SD	Standard gas Total	Weight	Mean difference IV, random, 95% CI
Dani et al. 2013	39	8	18	52	7	18	46.2%	−13.00 [−17.91, −8.09]
Li et al. 2014	32.4	3.1	19	39.1	6.8	17	53.8%	−6.70 [−10.22, −3.18]
Total (95% CI)			*37*			*35*	*100.0%*	*−9.61 [−15.76, −3.45]*

Heterogeneity: $\tau^2 = 15.09$; $\chi^2 = 4.18$, df = 1 ($P = 0.04$); $I^2 = 76\%$

Test for overall effect: $Z = 3.06$ ($P = 0.002$)

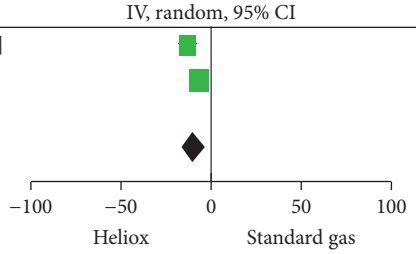


Figure 3: The comparison of Heliox versus standard air for the level of $PaCO_2$.

Study or subgroup	Heliox Events	Heliox Total	Standard gas Events	Standard gas Total	Weight	Risk ratio M-H, fixed, 95% CI
Colnaghi et al. 2012	3	27	10	24	55.6%	0.27 [0.08, 0.86]
Li et al. 2014	2	19	8	17	44.4%	0.22 [0.05, 0.91]
Total (95% CI)		*46*		*41*	*100.0%*	*0.25 [0.10, 0.61]*
Total events	5		18			

Heterogeneity: $\chi^2 = 0.04$, df = 1 ($P = 0.85$); $I^2 = 0\%$

Test for overall effect: $Z = 3.05$ ($P = 0.002$)

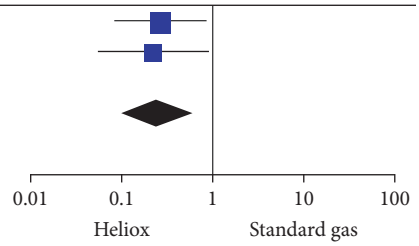


Figure 4: The comparison of Heliox versus standard air for the use of surfactant.

time of "need for mechanical ventilation" was different. The observation time of "failure of Heliox/standard gas" in the study by Dani et al. [11] was "during the 24 hours following extubation" and it was "within the first 7 days of life" in the study by Colnaghi et al. [12]. But the study by Li et al. [10] did not limit the observation time.

Although basic mechanisms by which Heliox improves efficacy are clear, a better understanding of its exact actions is needed. The possible mechanisms by which Heliox works are decreasing mean airway resistance and respiratory work, as well as improving gas exchange and lung compliance. Interestingly, Heliox might also have the potential for chemical benefits as an inert gas. The included RCT of Li et al. [10] showed that Heliox significantly reduced mean length of ventilation in comparison to standard gas, and the latter was positively correlated with interleukin-6 at baseline ($r = 0.474$, $P = 0.006$). Compared to animals ventilated with standard gas, levels of interleukin-8 and myeloperoxidase were also lower in animals ventilated with Heliox [8].

Prophylactic, early, and enough surfactant replacement therapy has been reported to reduce effectively the incidence of intubation and complications in preterm infants with RDS as compared with later selective surfactant administration [17]. However, the INSURE (intubation-surfactant-extubation) technique of surfactant administration is an invasive operation, and it is not successful in all preterm neonates with RDS, with a reported failure rate ranging from 19 to 69%. And the unsuccessful INSURE technique required subsequent intratracheal ventilation [18]. In our review with meta-analysis from two trials of Li et al. [10] and Colnaghi et al. [12], a remarkable decrease was demonstrated for the need of surfactant in the group of infants who received Heliox, and the difference was statistically significant. Our results further confirmed that Heliox was more successful than standard gas

Table 4: Pooled estimates for Heliox.

Secondary outcomes	Heliox versus standard gas						RR/mean difference (95% CI)	Heterogeneity	
	Colnaghi et al. 2012		Dani et al. 2013		Li et al. 2014				
	27	24	18	18	19	17		*P* value	I^2
Incidence of bronchopulmonary dysplasia	5	3	7	11	0	0	0.81 [0.38–1.73]	0.25	23%
Incidence of patent ductus arteriosus	12	10	16	16	7	5	1.06 [0.79–1.43]	0.82	0%
Incidence of retinopathy of prematurity	1	1	4	5	0	0	0.82 [0.28–2.34]	0.94	0%
Incidence of necrotizing enterocolitis	0	1	2	3	3	1	0.94 [0.30–2.91]	0.45	0%
Hospital stay (days)	52 ± 30	47 ± 33	115 ± 18	109 ± 15	—	—	5.78 [−3.06–14.63]	0.20	0%
Time of noninvasive ventilation (days)	26 ± 37	33 ± 6	—	—	1.6 ± 0.6	2.5 ± 1.0	−0.91 [−1.46–−0.36]	0.001	0%
Incidence of intraventricular hemorrhage	0	0	5	4	0	0	1.25 [0.40–3.91]	Not applicable	
Incidence of periventricular leukomalacia	0	0	2	1	0	0	2.00 [0.20–20.15]	Not applicable	
Death	0	0	3	2	0	0	1.50 [0.28–7.93]	Not applicable	

in preventing the INSURE-associated endotracheal intubation in the initial treatment of premature infants with RDS. Noninvasive respiratory support and Heliox therapy may have synergistic effects on uniform distribution of oxygen and carbon dioxide, as well as decreasing alveolar surface tension. With the optimal lung capacity, relatively constant airway, and alveolar pressure, the pulmonary gas distribution at a uniform state could cause maximally less alveolar excessive expansion or atelectasis and, hence, avoid injury of lung.

BPD is a complex disorder and remains the most common complication of very preterm infants [19]. Initiation and/or maintenance of endotracheal ventilation, especially during the first week of life, may activate the alveolar macrophages, leading to the release of proinflammatory cytokines. Exposure to oxygen with high concentrations actually also potentiates the inflammatory cascade. Moreover, ventilator-associated lung injuries may lead to the ongoing inflammation and oxidative stress in the lung, finally leading to BPD. Many studies have been done to compare the effects between Heliox and standard gas on BPD and the incidence of BPD. Szczapa et al. [20] reported that mechanical ventilation with Heliox resulted in the improvement of respiratory function and oxygenation in infants with severe BPD requiring mechanical ventilation. Wolfson et al. [21] also indicated that Heliox decreased the work of breathing and airway resistance and reduced respiratory muscle fatigue and caloric requirements for breathing, thus providing additional calories for growth and recovery. In our meta-analysis, pooling of data from the two trials of Dani et al. [11] and Colnaghi et al. [12] did not reveal the beneficial effects for decreasing the incidence of BPD as compared with standard gas. Although a similar result was found in the study by Elleau et al. [15], the latter should be reconsidered because the sample size of this study was small and it was reported in the presurfactant era.

In addition, our review also revealed that Heliox was related to the reduction of time of noninvasive ventilation. No heterogeneity has been found [10, 12].

Our review from two trials [11, 12] showed that Heliox could not shorten the duration of hospitalization as compared with the standard gas. Besides, Heliox did not show any benefit in decreasing the incidence of PDA, ROP, BPD, and NEC. No heterogeneity has been found among the trials.

Furthermore, several modes of noninvasive respiratory support were used in the three included trials, including NIPPV, CPAP, and BiPAP. Up to now, numerous studies and meta-analyses have compared the effects of noninvasive ventilation on the incidence of intubation and subsequent complications, and the results remained inconsistent [5, 22–25]. Therefore, the results of the meta-analysis could be affected by the selection of noninvasive ventilation strategies.

In our review from three trials [10–12], the times of Heliox administration were different, with 3 hours by Li et al. [10], 24 hours by Dani et al. [11], and 12 hours by Colnaghi et al. [12]. As Martinón-Torres [26] said, one important advantage (and disadvantage) of Heliox is that it works only while being administered, and some beneficial effects of Heliox can be noted soon after initiation for that particular patient. In contrast, once Heliox is withdrawn, the symptoms could be aggravated [20]. Besides the short-term effects in preterm infants, neonatologists are more concerned with the long-term benefits, especially in very preterm infants. Therefore, the optimal beneficial time of Heliox administration is

unclear and more trials are needed to verify it. Conclusions should be cautious because of the significant heterogeneity of administration time of Heliox among the studies. Szczapa et al. [20] proposed a question of how long Heliox should be continued and what should be set as the criteria for stopping it. One explanation was that Heliox should be continued during BPD exacerbation in order to minimize further lung injury associated with mechanical ventilation and stopped when lung function improved. The administration time of Heliox might be determined by the aim of used Heliox. For minimizing intubation in primary respiratory support, Heliox might be used for twelve to seventy-two hours [12], but, for avoiding reintubation and reducing the incidence of BPD, continued Heliox might be needed for more than eight days [15].

One important cause to explain the inconsistence among the included studies might be gestational age. In our review from three trials [10–12], the mean gestational ages were different, with 34.2 weeks by Li et al. [10], 25.4 weeks by Dani et al. [11], and 30.6 weeks by Colnaghi et al. [12]. Nowadays, preterm infants were actually divided into late preterm (34–36 weeks), moderate preterm (32-33 weeks), and very preterm (<32 weeks). In the very preterm infants, the incidence rate of RDS gradually has been confirmed to be increased with decreasing gestational age. EuroNeoStat figures for 2006 showed an incidence of 92% at 24-25 weeks, 88% at 26-27 weeks, 76% at 28-29 weeks, and 57% at 30-31 weeks of gestational age [1]. In the infants with gestational age less than 30 weeks, an obvious increase was observed in the incidence rate of RDS. It might therefore be improper to conduct the analysis in preterm infants with long time span, and preterm birth should be also divided into more subgroups according to the gestational age, such as 30–32 weeks, 28–32 weeks, and 26–28 weeks. Similarities also appeared in the complications of the secondary outcomes, and this was a main limitation in the analysis.

There were inconsistent results about side effects of Heliox administration in the previous studies. Szczapa et al. [20] indicated that mechanical ventilation with Heliox was feasible and could be applied without side effects in preterm infants with severe BPD. Spontaneously breathing Heliox could be tolerated in preterm infants with BPD [21]. Moreover, no side effects appeared even after eight days of administration of Heliox in preterm infants with RDS [15]. The above studies were in agreement with the comment of Martinón-Torres [26], in which no lines of evidence of harmful effects of Heliox were reported in 73 clinical trials. In the present review, there were also no side effects of Heliox in the three included trials. Actually, as far as the properties of helium are concerned, no side effects are a reasonable speculation. In contrast, several studies suggested side effects of Heliox. In a preliminary study designed to assess the tolerance to Heliox in infants with BPD, spontaneously breathing Heliox had immediate consequences such as wakening, crying, decrease in skin temperature, and hypoxia [27]. Similarly, hypoxia was also reported by Butt et al. [28]. More studies are needed to observe the possible side effects of Heliox. Therefore, more trials are also needed to verify them in the future.

Last but not least, the relatively high costs of Heliox administration should be considered [29]. Among the included trials, the average cost was similar. The cost of Heliox of "12 hours" was "EUR750" in the study by Colnaghi et al. [12] and that of "3 hours" was "EUR200" in the studies by Li et al. [10]. Possibly, recycled use of Heliox may be a better selection and further direction.

The major limitation of the present study was the small sample size, and trials with small sample size were more likely to show larger beneficial effects than trials with large sample size [30]. And these beneficial effects were consistent with the reports of Zhang et al. [31] and Papageorgiou et al. [32]. The authors thought that it might be due to the lower methodological quality in small trials. As far as we are concerned, the cause of inducing the differences between small trials and large trials might be the baseline differences of the included patients. An example was when the pregnancy-associated diseases of mothers were balanced completely; the results of the small sample trial [33] were consistent with the multicenter trial [24]. These problems could be overcome in additional multicenter studies with large sample size or more strict inclusion criteria in the small trials. Given the potential limitations, more trials are needed in the future.

5. Conclusions

In summary, the present study supports the updated lines of evidence. Based on the results, the present review provides several lines of evidence that noninvasive ventilation with Heliox is more successful than noninvasive ventilation with standard gas in avoiding invasive ventilation, when used for the treatment of preterm infants with RDS. However, it is also clear that data on clinical outcomes are limited. Therefore, any formal grading at this time is improper. Given these important limitations, further trials are needed to assess the use of Heliox.

Abbreviations

RDS: Respiratory distress syndrome
BPD: Bronchopulmonary dysplasia
PLV: Periventricular leukomalacia
IVH: Intraventricular hemorrhage
PDA: Patent ductus arteriosus
NEC: Necrotizing enterocolitis
ROP: Retinopathy of prematurity.

Competing Interests

The authors declare no competing interests regarding the publication of this paper.

Authors' Contributions

Chen Long conceptualized and designed the study and drafted and revised the initial manuscript. Wang Li and Li Wanwei reviewed the data and revised the initial manuscript. Li Jie carried out the initial analyses. Shi Yuan conceptualized and designed the study and revised the initial manuscript. All

authors have seen and approved the manuscript for publication. Li Jie and Shi Yuan contributed equally to this paper.

Acknowledgments

The authors thank Wang Weiwei for the valuable proofreading, which greatly improved the presentation of this article.

References

[1] D. G. Sweet, V. Carnielli, G. Greisen et al., "European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants—2013 update," *Neonatology*, vol. 103, no. 4, pp. 353–368, 2013.

[2] C. St Clair, E. R. Norwitz, K. Woensdregt et al., "The probability of neonatal respiratory distress syndrome as a function of gestational age and lecithin/sphingomyelin ratio," *American Journal of Perinatology*, vol. 25, no. 8, pp. 473–480, 2008.

[3] B. J. Stoll, N. I. Hansen, E. F. Bell et al., "Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network," *Pediatrics*, vol. 126, no. 3, pp. 443–456, 2010.

[4] B. Schmidt, E. V. Asztalos, R. S. Roberts, C. M. T. Robertson, R. S. Sauve, and M. F. Whitfield, "Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms," *Journal of the American Medical Association*, vol. 289, no. 9, pp. 1124–1129, 2003.

[5] W. Li, C. Long, H. Zhangxue et al., "Nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome: a meta-analysis and up-date," *Pediatric Pulmonology*, vol. 50, no. 4, pp. 402–409, 2015.

[6] A. Barach, "The use of helium in the treatment of asthma and obstructive lesions in the larynx and trachea," *Annals of Internal Medicine*, vol. 9, no. 6, pp. 739–765, 1935.

[7] F. Martinón Torres and J. M. Martinón Sánchez, "Heliox therapy," in *Mechanical Ventilation in Newborns, Infants and Children*, J. Casado Flores, Ed., pp. 265–274, Editorial Ergón, Madrid, Spain, 2nd edition, 2011.

[8] U. S. Nawab, S. M. Touch, T. Irwin-Sherman et al., "Heliox attenuates lung inflammation and structural alterations in acute lung injury," *Pediatric Pulmonology*, vol. 40, no. 6, pp. 524–532, 2005.

[9] J. P. T. Higgins and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions Version 4.2.6*, John Wiley & Sons, Chichester, UK, 2006.

[10] X. Li, J. Shen, J. Zhao, S. Tang, and Y. Shi, "Nasal intermittent positive pressure ventilation with heliox in premature infants with respiratory distress syndrome: a randomized controlled trial," *Indian Pediatrics*, vol. 51, no. 11, pp. 900–902, 2014.

[11] C. Dani, G. Fontanelli, I. Lori, F. Favelli, and C. Poggi, "Heliox non-invasive ventilation for preventing extubation failure in preterm infants," *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 26, no. 6, pp. 603–607, 2013.

[12] M. Colnaghi, M. Pierro, C. Migliori et al., "Nasal continuous positive airway pressure with heliox in preterm infants with respiratory distress syndrome," *Pediatrics*, vol. 129, no. 2, pp. e333–e338, 2012.

[13] C. Migliori, P. Gancia, E. Garzoli, V. Spinoni, and G. Chirico, "The effects of helium/oxygen mixture (heliox) before and after extubation in long-term mechanically ventilated very low birth weight infants," *Pediatrics*, vol. 123, no. 6, pp. 1524–1528, 2009.

[14] P. Stucki, P. Scalfaro, Q. de Halleux, F. Vermeulen, I. Rappaz, and J. Cotting, "Successful management of severe respiratory failure combining heliox with noninvasive high-frequency percussive ventilation," *Critical Care Medicine*, vol. 30, no. 3, pp. 692–694, 2002.

[15] C. Elleau, R.-I. Galperine, H. Guenard, and J.-L. Demarquez, "Helium-oxygen mixture in respiratory distress syndrome: a double-blind study," *The Journal of Pediatrics*, vol. 122, no. 1, pp. 132–136, 1993.

[16] J.-M. Liet, T. Ducruet, V. Gupta, and G. Cambonie, "Heliox inhalation therapy for bronchiolitis in infants," *Cochrane Database of Systematic Reviews*, vol. 18, no. 9, Article ID CD006915, 2015.

[17] T. P. Stevens, E. W. Harrington, M. Blennow, and R. F. Soll, "Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome," *Cochrane Database of Systematic Reviews*, no. 4, Article ID CD003063, 2007.

[18] G. Vento, R. Pastorino, L. Boni, F. Cota, V. Carnielli, and F. Cools, "Efficacy of a new technique—INtubate-RECruit-SURfactant-Extubate—'IN-REC-SUR-E'—in preterm neonates with respiratory distress syndrome: study protocol for a randomized controlled trial," *Trials*, vol. 17, article 414, 2016.

[19] A. H. Jobe, "The new bronchopulmonary dysplasia," *Current Opinion in Pediatrics*, vol. 23, no. 2, pp. 167–172, 2011.

[20] T. Szczapa, J. Gadzinowski, J. Moczko, and T. A. Merritt, "Heliox for mechanically ventilated newborns with bronchopulmonary dysplasia," *Archives of Disease in Childhood—Fetal and Neonatal Edition*, vol. 99, no. 2, pp. F128–F133, 2014.

[21] M. R. Wolfson, V. K. Bhutani, T. H. Shaffer, and F. W. Bowen Jr., "Mechanics and energetics of breathing helium in infants with bronchopulmonary dysplasia," *The Journal of Pediatrics*, vol. 104, no. 5, pp. 752–757, 1984.

[22] Y. Shi, S. Tang, J. Zhao, and J. Shen, "A prospective, randomized, controlled study of NIPPV versus nCPAP in preterm and term infants with respiratory distress syndrome," *Pediatric Pulmonology*, vol. 49, no. 7, pp. 673–678, 2014.

[23] J. Meneses, V. Bhandari, J. G. Alves, and D. Herrmann, "Noninvasive ventilation for respiratory distress syndrome: a randomized controlled trial," *Pediatrics*, vol. 127, no. 2, pp. 300–307, 2011.

[24] H. Kirpalani, D. Millar, B. Lemyre, B. A. Yoder, A. Chiu, and R. S. Roberts, "A trial comparing noninvasive ventilation strategies in preterm infants," *The New England Journal of Medicine*, vol. 369, no. 7, pp. 611–620, 2013.

[25] J. Meneses, V. Bhandari, and J. G. Alves, "Nasal intermittent positive-pressure ventilation vs nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome: a systematic review and meta-analysis," *Archives of Pediatrics and Adolescent Medicine*, vol. 166, no. 4, pp. 372–376, 2012.

[26] F. Martinón-Torres, "What's weighing down heliox?" *The Lancet Respiratory Medicine*, vol. 3, no. 1, pp. 14–15, 2015.

[27] E. De Gamarra, G. Moriette, M. Farhat, and H. Walti, "Heliox tolerance in spontaneously breathing neonates with bronchopulmonary dysplasia," *Biology of the Neonate*, vol. 74, no. 3, pp. 193–199, 1998.

[28] W. W. Butt, G. Koren, S. England et al., "Hypoxia associated with helium-oxygen therapy in neonates," *The Journal of Pediatrics*, vol. 106, no. 3, pp. 474–477, 1985.

[29] G. Valli, P. Paoletti, D. Savi, D. Martolini, and P. Palange, "Clinical use of heliox in asthma and COPD," *Monaldi Archives for Chest Disease—Pulmonary Series*, vol. 67, no. 3, pp. 159–164, 2007.

[30] J. A. C. Sterne and M. Egger, "Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis," *Journal of Clinical Epidemiology*, vol. 54, no. 10, pp. 1046–1055, 2001.

[31] Z. Zhang, X. Xu, and H. Ni, "Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study," *Critical Care*, vol. 17, no. 1, article R2, 2013.

[32] S. N. Papageorgiou, G. N. Antonoglou, E. Tsiranidou, S. Jepsen, and A. Jäger, "Bias and small-study effects influence treatment effect estimates: a meta-epidemiological study in oral medicine," *Journal of Clinical Epidemiology*, vol. 67, no. 9, pp. 984–992, 2014.

[33] L. Chen, L. Wang, J. Li, N. Wang, and Y. Shi, "Noninvasive ventilation for preterm twin neonates with respiratory distress syndrome: a randomized controlled trial," *Scientific Reports*, vol. 5, Article ID 14483, 2015.

Hindawi Publishing Corporation
Canadian Respiratory Journal
Volume 2016, Article ID 3915237, 13 pages
http://dx.doi.org/10.1155/2016/3915237

Review Article

Noninvasive Positive Pressure Ventilation in Chronic Heart Failure

Hao Jiang,[1] Yi Han,[2] Chenqi Xu,[1,3] Jun Pu,[1] and Ben He[1]

[1]*Department of Cardiovascular Diseases, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[2]*Department of Geriatrics, First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China*
[3]*Renal Division and Molecular Cell Laboratory for Kidney Disease, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Correspondence should be addressed to Jun Pu; pujun310@hotmail.com and Ben He; heben1025@hotmail.com

Received 3 June 2016; Revised 22 August 2016; Accepted 4 October 2016

Academic Editor: Zhongheng Zhang

Instruction and Objectives. Noninvasive positive pressure ventilation (NPPV) alleviates sleep-disordered breathing (SDB) and it may improve cardiac function in SDB patients. Because large randomized controlled trials directly evaluating the impact of NPPV on cardiac function are lacking, we conducted a meta-analysis of published data on effectiveness of NPPV in improving cardiac function in patients with chronic heart failure regardless of SDB presence. *Methods*. Controlled trials were identified in PubMed, OVID, and EMBASE databases. Both fixed and randomized models were used in meta-analysis with primary outcomes of left ventricular ejection fraction (LVEF). *Results*. Nineteen studies were included with a total of 843 patients. Compared to standard medical treatment (SMT) plus sham-NPPV or SMT only, NPPV plus SMT was associated with improvement in LVEF (weighted mean difference 5.34, 95% CI, [3.85, 6.82]; $P < 0.00001$) and plasma brain natriuretic peptide (BNP) level (weighted mean difference −117.37, 95% CI, [−227.22, −7.52]; $P = 0.04$) and no influence on overall mortality (RR 1.00, 95% CI, [0.96, 1.04]; $P = 0.95$). *Conclusions*. In the present meta-analysis, use of NPPV plus SMT improved LVEF and reduced plasma BNP level but did not improve overall mortality in patients with chronic heart failure.

1. Introduction

According to an estimate by the American Heart Association (AHA), 5.1 million American adults suffered from heart failure (HF) in 2014 [1]. Although survival has improved over time, 5-year mortality of HF patients remains high at about 50% [2–4]. HF also poses a large financial burden on the healthcare system amounting in 2012 to approximately 20.9 million dollars in direct medical costs in the United States [5].

Forty percent to half of patients with chronic heart failure (CHF) and impaired left ventricular function go on to develop sleep-disordered breathing (SDB), either obstructive or central sleep apnea (OSA or CSA) [6–9], both of which disrupt the normal relaxing effects of sleep on the cardiovascular system. Accumulated evidence suggested that SDB accelerates the progression of CHF. SDB induces hypoxia and hypercapnia, promotes autonomic imbalance with sympathetic activation and parasympathetic inhibition, and increases the blood pressure and left ventricular afterload, all of which are stimuli to myocardial ischemia [10–12], adverse cardiac remodeling [13–15], and left ventricular dysfunction [16, 17]. Among the modalities of noninvasive positive pressure ventilation (NPPV) used to treat SDB in CHF patients, continuous positive airway pressure (cPAP) attenuates central sleep apnea, improves nocturnal oxygenation and left ventricular systolic function, and reduces excitability of the overactivated sympathetic nervous system [18–21]. The more recent adaptive servoventilation (ASV) also alleviates SDB and it may improve cardiac function in CHF patients [22–27].

Perhaps because of limitations in sample size, incomplete data reporting, and population differences, not all studies on NPPV have yielded positive results in terms of cardiac function improvement. For instance, Pepperell et al. found no difference in change in left ventricular ejection fraction (LVEF) between ASV treated patients and controls [25]; Egea

et al. found no significant improvement in 6 min walking test between the cPAP and control groups [28]; and both Ferrier et al. and Hastings et al. found that neither cPAP nor ASV significantly decreased plasma BNP concentration [29, 30].

We therefore sought to explore in a meta-analysis if adult patients with CHF would benefit from NPPV in improving cardiac function, in the form of cPAP or ASV, as compared to standard medical treatment (SMT).

2. Methods

2.1. Search Strategy and Literature Screening. A systematic literature review was undertaken on January 26th, 2015, using PubMed, OVID, and EMBASE databases. To retrieve the largest number of potentially related studies, the following terms were used individually: "noninvasive positive pressure ventilation," "continuous positive airway pressure," "bilevel positive airway pressure," "adaptive servo-ventilation," and "heart failure." Articles were first screened by title and abstract, and reviews, meta-analyses, guidelines, letters, case reports, clinical trials in children, newborns, or postsurgical patients, and animal experiments were excluded. Three studies with full texts not written in English also were excluded.

The following criteria then were used to identify potentially suitable studies in a second screen: the trials were (a) well-designed randomized controlled trials (RCTs), quasirandomized controlled trials (qRCTs), and nonrandomized controlled trials; (b) enrolled subjects were adults older than 18 years and diagnosed with chronic heart failure, with or without sleep-disordered breathing (SDB); and (c) the intervention was noninvasive positive pressure ventilation (NPPV) in the form of continuous positive airway pressure (cPAP), adaptive servoventilation (ASV), or bilevel positive airway pressure (BiPAP), plus standard medical treatment (SMT), while the control treatment was SMT plus sham-NPPV or SMT only; and (d) left ventricular ejection fraction (LVEF) must be included in the study outcomes.

After the above-mentioned screening, the authors obtained the full text articles and read them carefully and independently. Articles meeting the following criteria were excluded: (a) follow-up period was less than 4 weeks; (b) number of study participants was less than 10; (c) crossover-design was excluded if data before washout were not reported or unavailable; (d) outcome LVEF was only reported by a descriptive conclusion (original data or processed data were not reported or available); and (e) subjects from subgroup analysis of the other clinical trials were repeatedly counted. In addition, we excluded articles including BiPAP from the final analysis because BiPAP worsens, rather than improves, central apneas [31].

2.2. Data Extraction and Processing. Two authors extracted data independently. Descriptive data include first author, publication year, study design, duration of study arms, duration of washout (if applicable), type of control used, HF inclusion criteria, SDB inclusion criteria, proportion of male patients, mean age, and mean BMI (if available). For outcome data, the mean together with standard deviation (SD) at baseline and end-trial time point was extracted for the NPPV and control arms. Standard error of the mean (SEM) was converted into SD. The change in mean was calculated as end-trial value minus baseline value. Variables reported in interquartile range were converted into mean using the method provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.0.1) [32]. The change in SD was calculated using the formula also provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.0.1) [32]. For the present meta-analysis, BNP was expressed in pg/mL using the conversion factor provided by Weber and Hamm [33] when different units were used. Events were defined as refractory heart failure and worsening heart failure if (1) events reported as refractory heart failure, or (2) events reported as heart failure worsening after NPPV application, or (3) events reported as unstable need emergency transplantation and readmission due to heart failure worsening. In particular, for outcome in crossover studies, the mean and variability in the NPPV and control arms before washout were extracted (if available) in this article.

2.3. Data Analysis. Two authors (Chenqi Xu and Hao Jiang) conducted the analyses using Review Manager version 5.2 (Nordic Cochrane Center). The pooled estimate of mean weight difference (MWD) or risk ratio (RR) with their 95% CI was calculated using random effect model or fixed effect model according to heterogeneity among studies. Q value and I^2 statistics, calculated when the number of analyzed studies exceeded three, were used as heterogeneity measures. A fixed effect model was used if there was no significant heterogeneity ($I^2 < 50\%$); otherwise, the random effects model would be applied for meta-analysis. A forest plot was constructed based on the results of pooled analysis of the NPPV and control arms. The primary outcome of this meta-analysis was LVEF. Subgroup analysis based on the degree of LVEF and reported geographical location was performed. Moreover, sensitivity analyses were performed to identify the effect of a single trial by sequential elimination of each trial from the pool and then to assess the overall outcomes. Statistical significance was set at P value < 0.05. Risk of bias was evaluated carefully and tabulated with brief details by Jun Pu, M.D.

3. Results

3.1. Literature Search. In a search of the PubMed database, 1478 potential articles were identified. After applying the prespecified exclusion and inclusion criteria, the full texts of 75 articles were read, yielding 23 eligible studies. During data extraction and analysis, 4 additional studies were excluded for different reasons: Smith et al. (2007) [34] did not report the mean and variability before washout; Zhang et al. (2006) [35] conducted a trial over a period of 1 week, which was too short to meet the inclusion criteria; Gilman et al. (2008) [36] entailed a subgroup analysis of the CANPAP trial, that is, a redundant population; and Campbell et al. (2011)'s study included a population that was not large enough. Finally, 19 studies were included in the pooled analysis. The study

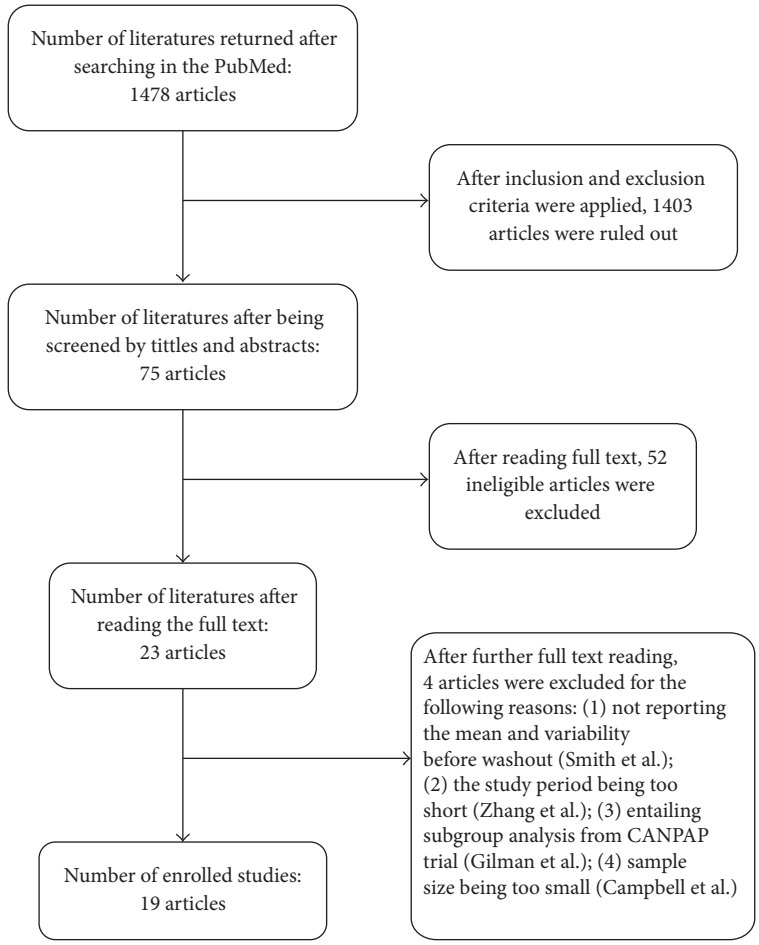


Figure 1: Literature screening flow.

selection process is outlined in Figure 1. Characteristics of the included 19 studies are presented in Table 1. The risk of bias is presented in Figure 2. The included studies showed relatively high quality with an acceptable risk of bias overall (Figure 2(a)). However, there was high performance risk and detection bias in most of the studies (Figure 2(b)).

3.2. Meta-Analysis

3.2.1. Left Ventricular Ejection Fraction (LVEF). The weighted mean difference of the total is 5.34 favoring NPPV (95% CI, [3.85, 6.82]; $P < 0.00001$). Heterogeneity between the studies was significant ($Q = 41.0$, $P = 0.002$), and I^2 was 56%. When the study by Bradley et al. (2005) [37] was removed from the pooled analysis, I^2 changed from 56% to 33%.

The weighted mean difference of the cPAP subgroup was 3.85 favoring cPAP (95% CI, [2.28, 5.42]; $P < 0.00001$). Heterogeneity among studies in the cPAP subgroup was not significant ($Q = 14.59$, $P = 0.15$), with I^2 of 31%.

The weighted mean difference of the ASV subgroup was 6.83 favoring ASV (95% CI, [4.46, 9.19]; $P < 0.00001$). Heterogeneity among studies in the ASV subgroup was significant ($Q = 15.11$, $P = 0.03$), with I^2 of 54% (see Figure 3).

The weighted mean difference of LVEF < 30% was 4.94 favoring NPPV (95% CI, [2.78, 7.10]; $P < 0.00001$). Heterogeneity among studies in the LVEF < 30% subgroup was significant ($Q = 19.95$, $P = 0.006$), with I^2 of 65%.

The weighted mean difference of LVEF > 30% was 5.73 favoring NPPV (95% CI, [4.03, 7.44]; $P < 0.00001$). Heterogeneity among studies in the LVEF > 30% subgroup was not significant ($Q = 12.39$, $P = 0.26$), with I^2 of 19%.

The weighted mean difference of the European subgroup was 5.05 favoring ASV (95% CI, [0.07, 10.03]; $P = 0.05$). Heterogeneity among studies in the ASV subgroup was significant ($Q = 4.96$, $P = 0.08$), with I^2 of 60%.

The weighted mean difference of the Asian subgroup was 7.92 favoring ASV (95% CI, [5.58, 9.96]; $P = 0.05$). Heterogeneity among studies in the ASV subgroup was not significant ($Q = 2.43$, $P < 0.00001$), with I^2 of 8.7%.

3.2.2. Left Ventricular End-Diastolic Dimension (LVEDD). Five studies reported data on change in LVEDD between before and after intervention. The weighted mean difference

Table 1: Characteristics of 19 studies included in meta-analysis.

Study	Length of follow-up	Location	Ventilator mode	Ventilator parameters	Ventilator connection method	Patients	Control	Trial n (m/f), age (ys)	Control n (m/f), age	Results
Arzt et al. 2005	3 months	Germany	CPAP	CPAP: 8 to 12 cm H_2O	Face mask	CHF with CSA	Nasal oxygen treatment	14 (NP), 64.0 ± 2	10 (NP), 65.0 ± 2	Ventilatory efficiency LVEF
Bradley et al. 2005	2 years	Canada	CPAP	CPAP: 10 cm H_2O	Face mask	CHF with CSA	SMT	128 (125/3), 63.2 ± 9.1	130 (123/7), 63.5 ± 9.8	Effect of CPAP on CSA and LVEF Death rates
Egea et al. 2008	3 months	Spain	CPAP	NP	Face mask	CHF with SA	Sham-CPAP	28 (24/4), 64.0 ± 0.9	32 (29/3), 63.0 ± 1.6	AHI and LVEF
Ferrier et al. 2008	6 months	New Zealand	CPAP	NP	Face mask	CHF with OSA	SMT	19 (16/3), 58.5 ± 11.2	7 (3/4), 60.3 ± 4.3	LVEF, SBP, BNP, LVESD, LVEDD
Granton et al. 1996	3 months	Canada	NCPAP	CPAP: 10 to 12.5 cm H_2O	Nasal mask	CHF with CSR-CSA	SMT	9 (NP), 58.3 ± 2.2	8 (NP), 58.0 ± 2.0	MIP and MEP, LVEF, dyspnea
Haruki et al. 2011	6 months	Japan	ASV	EPAP: 5 cm H_2O IPAP: 3–10 cm H_2O	Face mask	CHF	SMT	15 (11/4), 67.0 ± 11.0	11 (8/3), 67.0 ± 14.0	LVEF, LVEDV, LVESV
Hastings et al. 2010	6 months	United Kingdom	ASV	NP	Face mask	CHF with SA	SMT	11 (NP), 61.3 ± 10.0	8 (NP), 64.5 ± 8.0	AHI, LVEF, BNP
Johnson et al. 2008	6.9 ± 3.3 months	Canada and United States	CPAP	CPAP: 10.6 ± 1.6 cm H_2O	Nasal mask Face mask	CHF with OSA	SMT	7 (7/0), 61.0 ± 12.0	5 (5/0), 62.0 ± 9.0	Stroke volume, LVEF, LVEDV, LVESV
Joho et al. 2012	3.5 ± 0.8 months	Japan	ASV	EPAP: 4-5 cm H_2O IPAP: 3–10 cm H_2O	Face mask	CHF with CSA	SMT	20 (18/2), 62.0 ± 11.0	12 (10/2), 68.0 ± 9.0	LVEF, LVDd, LVDs, BNP, MSNA
Kaneko et al. 2003	1 month	Canada	CPAP	CPAP: 8.9 ± 0.7 cm H_2O	NP	CHF with OSA	SMT	12 (11/1), 55.9 ± 2.5	12 (10/2), 55.2 ± 3.6	BP, HR, LVESD, LVEDD, LVEF
Koyama et al. 2010	1 month	Japan	ASV	EPAP: 4 cm H_2O IPAP: 3–10 cm H_2O	NP	CHF with SDB	SMT	10 (8/2), 68.4 ± 4.0	7 (4/3), 71.4 ± 7.6	AHI hs-CRP BNP LVEF

Table 1: Continued.

Study	Length of follow-up	Location	Ventilator mode	Ventilator parameters	Ventilator connection method	Patients	Control	Trial n (m/f), age (ys)	Control n (m/f), age	Results
Koyama et al. 2011	12 months	Japan	ASV	EPAP: 5 cm H_2O IPAP: 3–10 cm H_2O	NP	CHF with SDB	SMT	27 (23/4), 74.8 ± 7.6	16 (13/3), 75.4 ± 6.4	eGFRhs-CRP, LVEF
Mansfield et al. 2004	3 months	Australia	CPAP	CPAP: 8.8 ± 1.4 mm Hg	Nasal mask	CHF with OSA	SMT	28 (28/0), 57.2 ± 1.7	27 (24/3), 57.5 ± 1.6	LVEF, UNE
Naughton et al. 1995	1 month	Canada	NCPAP	CPAP: 10 to 12.5 cm H_2O	Nasal mask	CHF with CSR-CSA	SMT	12 (NP), 61.0 ± 3.2	12 (NP), 56.6 ± 3.2	LVEF effect of NCPAP on CSA
Oldenburg et al. 2011	12 months	Germany	ASV	EPAP: 4-5 cm H_2O IPAP: 3–10 cm H_2O	Face mask	CHF with CSR	SMT and CPAP noncompliance	56 (54/2), 67.7 ± 9.5	59 (52/7), 62.5 ± 11.8	NT-proBNP LVEF parameters of SDB
Pepperell et al. 2003	1 month	United Kingdom	ASV	EPAP: 5 cm H_2O IPAP: 3–10 cm H_2O	NP	CHF with CSR	Subtherapeutic ASV	15 (15/0), 71.4 ± 8.6	15 (14/1), 70.9 ± 7.9	Osler test BNP
Tkacova et al. 1997	1 month	Canada	CPAP	CPAP: 10 to 12.5 cm H_2O	Nasal mask	CHF with CSR-CSA	SMT	9 (NP), 61.0 ± 1.9	8 (NP), 58.6 ± 2.4	LVEF, ANP, MRF
Usui et al. 2005	1 month	Canada	CPAP	CPAP: 7.5 ± 0.5 cm H_2O	NP	CHF with OSA	SMT	8 (8/0), 55.0 ± 2.0	9 (7/2), 52.2 ± 4.1	MSNA, BP, HR, LVEF
Yoshihisa et al. 2011	6 months	Japan	ASV	EPAP: 4–10 mm Hg IPAP: 4–20 mm Hg	NP	CHF with CSR-CSA	SMT	23 (20/3), 60.8 ± 13.7	37 (29/8), 60.5 ± 16.7	LVEF BNP cardiac systolic and diastolic function

CPAP: continuous positive airway pressure; ASV: adaptive servoventilation; EPAP: expiratory positive airway pressure; IPAP: inspiratory positive airway pressure; NP: not provided; CHF: chronic heart failure; OSA: obstructive sleep apnea; CSR: Cheyne-Stokes respiration; CSA: central sleep apnea; SA: sleep apnea; SDB: sleep-disordered breathing; SMT: standard medical treatment; LVEF: left ventricular ejection fraction; MSNA: muscle sympathetic nerve activity; BNP: B-type natriuretic peptide; AHI: apnea/hypopnea index; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C- reactive protein; ANP: atrial natriuretic peptide; UNE: urinary norepinephrine; BP: blood pressure; HR: heart rate; MIP: maximal inspiratory pressure; MEP: maximal inspiratory pressure; LVESD: left ventricular end-systolic diameter; LVEDD: left ventricular end-diastolic dimension; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVDd: left ventricular end-diastolic dimension; LVDs: left ventricular end-systolic dimension.

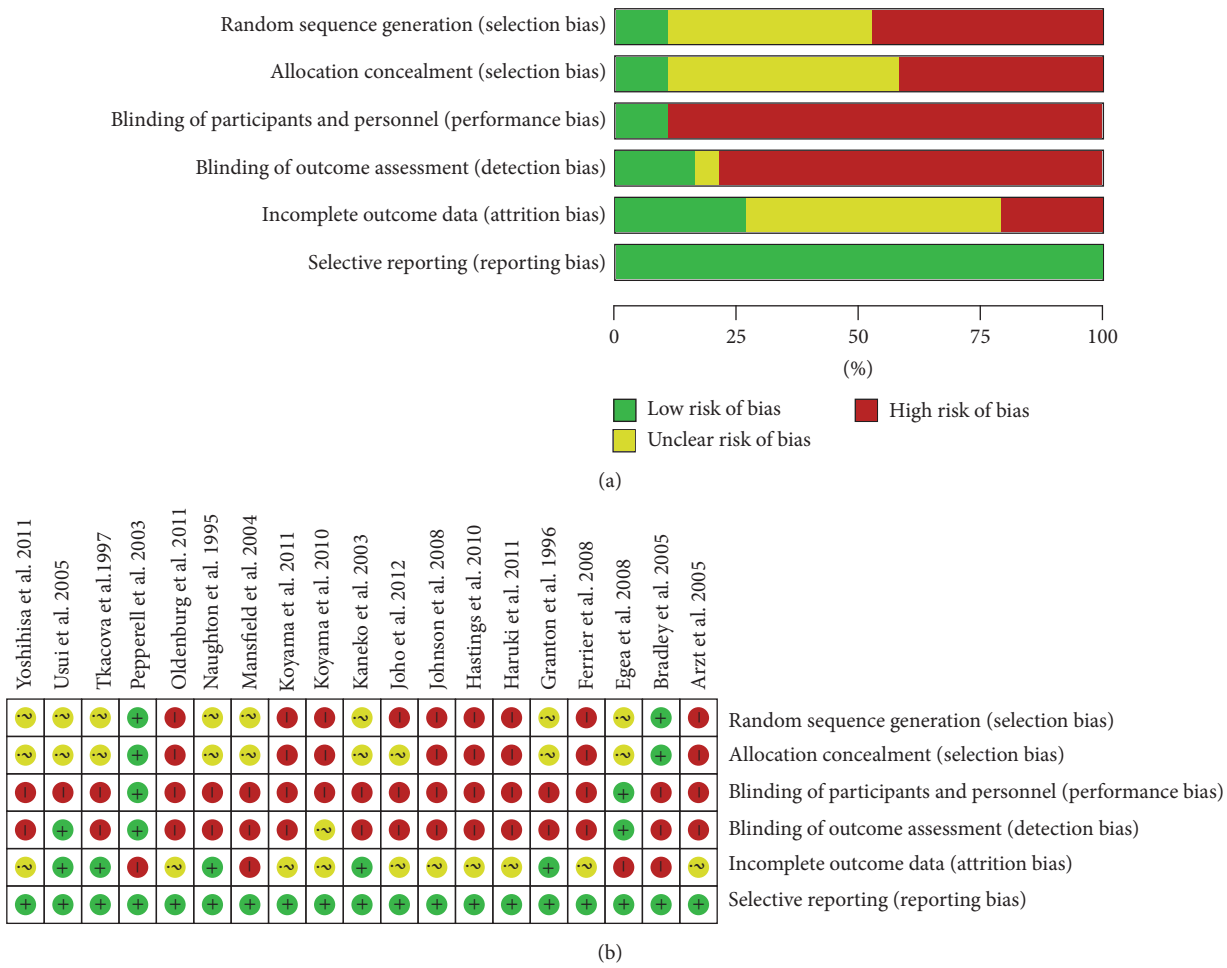


Figure 2: Risk of bias of the included studies. (a) Risk of bias graph; (b) risk of bias summary.

of the total was −1.91 favoring NPPV (95% CI, [−4.60, 0.78]; $P = 0.16$). Heterogeneity among studies was not significant ($Q = 8.13$, $P = 0.09$).

The weighted mean difference of the cPAP subgroup was 0.45 favoring control (95% CI, [−6.0, 6.89]; $P = 0.89$). Heterogeneity among studies in the cPAP subgroup was significant ($Q = 3.79$, $P = 0.05$), with I^2 of 74%.

The weighted mean difference of the ASV subgroup was −3.60 favoring ASV (95% CI, [−5.19, −1.50]; $P = 0.0008$). Heterogeneity among studies in the ASV subgroup was small ($Q = 1.39$, $P = 0.5$), with I^2 of 0%.

3.2.3. Plasma BNP Level. Six studies reported data on plasma BNP level before and after intervention; 5 from the ASV subgroup and one from the cPAP subgroup. The weighted mean difference of the total was −117.37 favoring NPPV (95% CI, [−227.22, −7.52]; $P = 0.04$). Heterogeneity among studies was significant ($Q = 26.40$, $P < 0.0001$), with I^2 of 81%.

The mean difference of the cPAP subgroup was 4.50, not significantly favoring the control (95% CI, [−77.12, 86.12]; $P = 0.91$). And the weighted mean difference of the ASV subgroup was −152.58 favoring ASV (95% CI, [−295.81, −9.35]; $P = 0.04$). Heterogeneity among studies in the ASV subgroup was significant ($Q = 26.40$, $P = 0.0001$), with I^2 of 83%.

3.2.4. Overall Mortality. In 19 trials involving 913 patients, we did not find difference in overall mortality between patients treated with NPPV plus standard medical treatment (SMT) and with SMT alone (RR 1.00, 95% CI, [0.96, 1.04]; $P = 0.95$) (Figure 4).

3.2.5. Adverse Events. Refractory heart failure and worsening heart failure: of the 19 studies included, 6 reported the events as defined. We found no difference in the incidence of refractory heart failure and worsening heart failure between patients treated with NPPV plus SMT and SMT alone (RR 1.07, 95% CI, [0.95, 1.21]; $P = 0.25$).

Cardiac arrest: 3 studies reported the incidence of cardiac arrest and we found no difference in the incidence of cardiac arrest between the two groups (RR 1.02, 95% CI, [0.93, 1.12]; $P = 0.63$).

Angina and acute myocardial infarction (AMI): 3 studies reported the incidence of angina and AMI. We found no difference in the incidence of angina and AMI between the two groups (RR 1.01, 95% CI, [0.95, 1.08]; $P = 0.64$).

Study or subgroup	NPPV Mean	NPPV SD	NPPV Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, random, 95% CI	Year
1.1.1 cPAP in LVEF									
Naughton et al.	7.7	10.9	12	−0.5	5.6	12	3.3%	8.20 [1.27, 15.13]	1995
Granton et al.	8.6	12.5	9	−1.1	5.4	8	2.2%	9.70 [0.72, 18.68]	1996
Tkacova et al.	8	9.5	9	−0.5	5.5	8	3.1%	8.50 [1.22, 15. 78]	1997
Kaneko et al.	8.8	5.8	12	1.5	4.4	12	6.3%	7.30 [3.18, 11.42]	2003
Mansfield et al.	5	9.9	19	1.5	8.5	21	4.3%	3.50 [−2.25, 9.25]	2004
Usui et al.	6.2	6.8	8	2.2	17	9	1.3%	4.00 [−8.06, 16.06]	2005
Bradley et al.	2.2	5.4	130	0.4	5.3	128	11.1%	1.80 [0.49, 3.11]	2005
Arzt et al.	4	6.1	14	1.6	4.7	10	6.0%	2.40 [−1.92, 6.72]	2005
Johnson et al.	5	2.9	7	0.7	4.7	5	5.5%	4.30 [−0.35, 8.95]	2008
Egea et al.	2.5	5.2	28	0	5.8	32	8.5%	2.50 [−0.28, 5.28]	2008
Ferrier et al.	4.7	2.9	7	0.7	4.7	5	5.5%	4.00 [−0.65, 8.65]	2008
Subtotal (95% CI)			*255*			*250*	*57.2%*	*3.85 [2.28, 5.42]*	
Heterogeneity: $\tau^2 = 1.87$; $\chi^2 = 14.59$, df = 10 ($P = 0.15$); $I^2 = 31\%$									
Test for overall effect: $Z = 4.82$ ($P < 0.00001$)									
1.1.2 ASV in LVEF									
Pepperell et al.	1.8	7.8	15	0.6	9.4	11	3.4%	1.20 [−5.61, 8.01]	2003
Hastings et al.	7.9	10	11	−4.8	8.3	8	2.6%	12.70 [4.45, 20.95]	2010
Koyama et al.	9.8	4	10	−0.1	6.1	7	4.9%	9.90 [4.75, 15.05]	2010
Koyama et al.	4.5	4.3	27	−2.3	5.8	16	7.6%	6.80 [3.53, 10.07]	2011
Oldenburg et al.	4.1	5.4	56	0.3	5.2	59	10.0%	3.80 [1.86, 5.74]	2011
Yoshihisa et al.	8.1	11.1	23	2.3	8.9	37	4.7%	5.80 [0.43, 11.17]	2011
Haruki et al.	13	8.4	15	5	7.8	11	3.8%	8.00 [1.73, 14.27]	2011
Joho et al.	7	7.2	20	−3	5.7	12	5.7%	10.00 [5.49, 14.51]	2012
Subtotal (95% CI)			*177*			*161*	*42.8%*	*6.83 [4.46, 9.19]*	
Heterogeneity: $\tau^2 = 5.50$; $\chi^2 = 15.11$, df = 7 ($P = 0.03$); $I^2 = 54\%$									
Test for overall effect: $Z = 5.67$ ($P < 0.00001$)									
Total (95% CI)			*432*			*411*	*100.0%*	*5.34 [3.85, 6.82]*	
Heterogeneity: $\tau^2 = 4.77$; $\chi^2 = 41.00$, df = 18 ($P = 0.002$); $I^2 = 56\%$									
Test for overall effect: $Z = 7.03$ ($P < 0.00001$)									
Test for subgroup differences: $\chi^2 = 4.23$, df = 1 ($P = 0.04$); $I^2 = 76.3\%$									

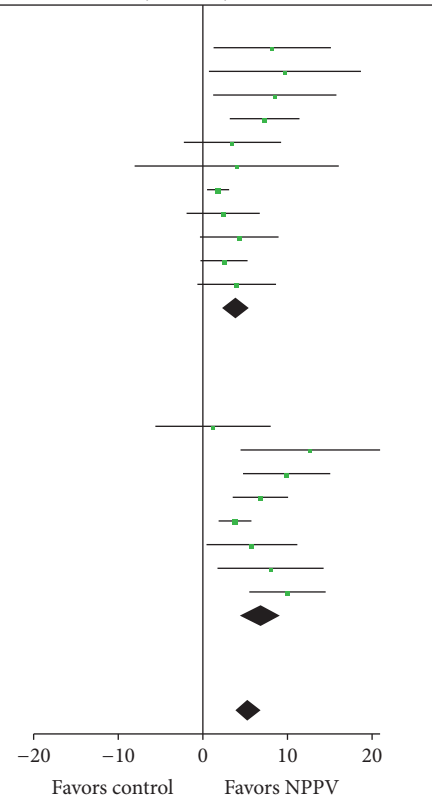


Figure 3: Forest plot of the effect of noninvasive positive airway pressure (cPAP and ASV) therapy for chronic heart failure on left ventricular ejection fraction (LVEF). CI: confidence interval; IV: inverse variance; SD: standard deviation; MD: mean difference.

3.2.6. Sensitivity Analysis. Sensitivity analyses by sequentially dropping individual trials and then evaluating the overall outcomes failed to identify any of the individual trials as having influenced the primary outcomes of the present meta-analysis to a significant extent (Table 2).

4. Discussion

Two main conclusions can be drawn for the present meta-analysis. Firstly, NPPV plus standard medical treatment (SMT) improved LVEF but did not improve overall mortality. Secondly, relative to SMT plus sham-NPPV/SMT alone, NPPV improved plasma BNP level but did not improve LVEDD and decrease threats of cardiac arrest events, angina, and AMI events.

4.1. Primary Outcomes

4.1.1. NPPV Improves LVEF in Chronic Heart Failure Patients. The present meta-analysis revealed that NPPV improves cardiac function by increasing LVEF. Among included studies, the majority of patients already had reduced LVEF or were in the course of developing heart failure with reduced LVEF and therefore were considered more likely to benefit from the use of NPPV. The results are consistent with those of many previous studies [19, 20, 30, 37–45]. However, several studies [21, 25, 28, 29, 46–48], most nonrandomized and with small sample sizes, showed that NPPV had no significant effects on the improvement of the cardiac function.

In our analyses, the weighted mean difference of the cPAP subgroup was 3.85 favoring cPAP, while that of the ASV subgroup was 6.83 favoring ASV. This might indicate that ASV is better than cPAP in the improvement of LVEF. However, the conclusion did not come from the direct comparison of cPAP and ASV since none of the included studies presented such a direct comparison. Interestingly, two randomized controlled trials showed that CHF patients with SDB might gain greater benefit from treatment with ASV than with CPAP [26, 49], which was consistent with our results.

The total heterogeneity of the aforementioned part of the analysis is significant (Figure 5). In the cPAP subgroup, the subtotal heterogeneity is not significant ($I^2 = 31\%$), while that of ASV subgroup is significant ($I^2 = 54\%$). To gain further insight into the heterogeneity, we performed subgroup analyses. Firstly, we used LVEF < 30% and LVEF > 30% as grouping criteria. Then, we found that when the mean LVEF of the NPPV group before intervention exceeded 30%, the weighted mean difference was favoring NPPV and the heterogeneity was small. However, when the mean LVEF of the NPPV group

Study or subgroup	NPPV Events	NPPV Total	Control Events	Control Total	Weight	Risk ratio (nonevent) M-H, fixed, 95% CI	Year
1.9.1 cPAP in total death rate							
Naughton et al.	0	14	0	15	3.6%	1.00 [0.88, 1.14]	1995
Granton et al.	0	9	0	8	2.1%	1.00 [0.81, 1.24]	1996
Tkacova et al.	0	9	0	8	2.1%	1.00 [0.81, 1.24]	1997
Kaneko et al.	0	12	0	12	3.0%	1.00 [0.86, 1.17]	2003
Mansfield et al.	2	28	0	27	6.7%	0.93 [0.82, 1.05]	2004
Arzt et al.	0	16	0	10	3.0%	1.00 [0.86, 1.17]	2005
Bradley et al.	27	130	28	128	24.0%	1.01 [0.89, 1.15]	2005
Usui et al.	0	8	0	9	2.1%	1.00 [0.81, 1.24]	2005
Johnson et al.	0	7	0	5	1.5%	1.00 [0.74, 1.35]	2008
Egea et al.	0	35	1	38	8.6%	1.03 [0.95, 1.10]	2008
Ferrier et al.	0	19	0	7	2.5%	1.00 [0.83, 1.21]	2008
Subtotal (95% CI)		*287*		*267*	*59.2%*	*1.00 [0.94, 1.06]*	
Total events	29		29				
Heterogeneity: $\chi^2 = 1.83$, df = 10 ($P = 1.00$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.05$ ($P = 0.96$)							
1.9.2 ASV in total death rate							
Pepperell et al.	0	15	0	15	3.7%	1.00 [0.88, 1.13]	2003
Koyama et al.	0	10	0	7	2.1%	1.00 [0.80, 1.25]	2010
Hastings et al.	0	11	0	8	2.3%	1.00 [0.82, 1.22]	2010
Haruki et al.	0	15	0	15	3.7%	1.00 [0.88, 1.13]	2011
Oldenburg et al.	5	66	3	62	14.5%	0.97 [0.89, 1.06]	2011
Koyama et al.	0	27	0	16	4.9%	1.00 [0.91, 1.10]	2011
Yoshihisa et al.	1	23	4	37	6.0%	1.07 [0.93, 1.24]	2011
Joho et al.	0	20	0	12	3.7%	1.00 [0.88, 1.14]	2012
Subtotal (95% CI)		*187*		*172*	*40.8%*	*1.00 [0.95, 1.05]*	
Total events	6		7				
Heterogeneity: $\chi^2 = 1.35$, df = 7 ($P = 0.99$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.02$ ($P = 0.98$)							
Total (95% CI)		*474*		*493*	*100.0%*	*1.00 [0.96, 1.04]*	
Total events	35		36				
Heterogeneity: $\chi^2 = 3.18$, df = 18 ($P = 1.00$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.06$ ($P = 0.95$)							
Test for subgroup differences: $\chi^2 = 0.00$, df = 1 ($P = 0.98$); $I^2 = 0\%$							

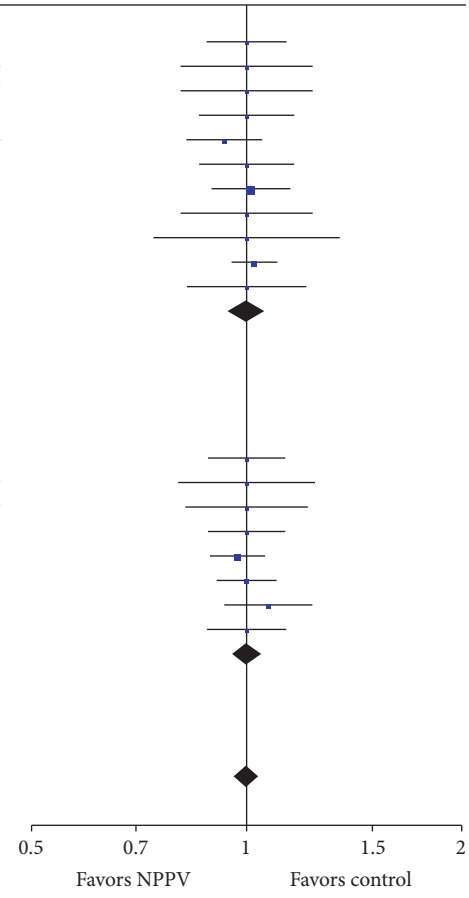


Figure 4: Forest plot of the effect of noninvasive positive airway pressure (cPAP and ASV) therapy for chronic heart failure on total mortality. CI: confidence interval; M-H: inverse variance; RR: risk ratio.

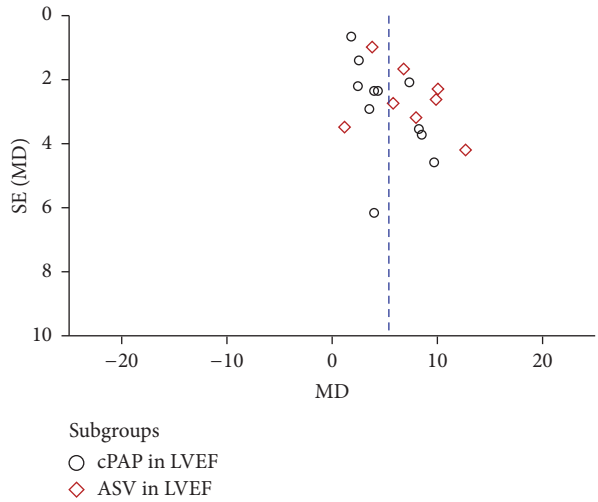


Figure 5: Funnel plot of NPPV on LVEF.

before intervention was 30% or less, the heterogeneity was significant. The latter result probably indicated a worse status among enrolled subjects with an LVEF of 30% or less, in turn leading to a worse prognosis and underlying a statistically significant heterogeneity.

Secondly, we analyzed the difference in LVEF-change among study regions for the ASV subgroup. According to the reported geographical location where the study was conducted, we divided the 8 studies into the European subgroup (3 studies, 2 in UK, and 1 in Spain) and Asian subgroup (5 studies, all in Japan). We found that the Asian subgroup's heterogeneity was small ($Q = 2.43$, $I^2 = 0\%$), while the heterogeneity of the European subgroup was significant ($Q = 4.96$, $I^2 = 60\%$). The regional disparity, the difference between medical care systems, and even the different races of patients may underlie the observations in the present study, which warrant further study.

4.1.2. NPPV Did Not Improve Mortality. According to the result of the analysis, the use of NPPV plus SMT did not improve overall mortality among patients with chronic heart failure. The analysis showed good homogeneity among all 19 studies enrolled ($Q = 3.18$, $I^2 = 0\%$) (Figure 6). Moreover, NPPV did not decrease cardiac adverse events in patients

Table 2: Sensitivity analysis showing the effect sizes for the primary outcomes after removing individual trials included in the meta-analysis.

	LVEF		Overall mortality	
	MD [95% CI]	*P* value	RR [95% CI]	*P* value
All trials	RE: 5.34 [3.85, 6.82]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.89 [3.08, 4.69]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Naughton et al. 1995 omitted	RE: 5.24 [3.72, 6.75]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.83 [3.02, 4.64]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Granton et al. 1996 omitted	RE: 5.23 [3.73, 6.73]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.84 [3.03, 4.65]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Tkacova et al. 1997 omitted	RE: 5.23 [3.72, 6.74]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.83 [3.02, 4.64]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Kaneko et al. 2003	RE: 5.19 [3.67, 6.72]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.75 [2.93, 4.57]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Mansfield et al. 2004	RE: 5.45 [3.90, 7.00]	<0.00001	RE: 1.01 [0.97, 1.04]	0.74
	FE: 3.89 [3.08, 4.70]	<0.00001	FE: 1.01 [0.97, 1.05]	0.77
Bradley et al. 2005	RE: 5.63 [4.25, 7.00]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 5.15 [4.14, 6.17]	<0.00001	FE: 1.00 [0.96, 1.03]	0.86
Usui et al. 2005	RE: 5.37 [3.85, 6.89]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.89 [3.08, 4.69]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Arzt et al. 2005	RE: 5.55 [3.99, 7.12]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.94 [3.12, 4.76]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Egea et al. 2008	RE: 5.64 [4.04, 7.24]	<0.00001	RE: 1.00 [0.96, 1.03]	0.79
	FE: 4.01 [3.17, 4.85]	<0.00001	FE: 1.00 [0.96, 1.04]	0.96
Johnson et al. 2008	RE: 5.43 [3.86, 7.00]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.87 [3.06, 4.69]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Ferrier et al. 2008	RE: 5.45 [3.88, 7.01]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.88 [3.07, 4.70]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Pepperell et al. 2003	RE: 5.50 [3.97, 7.03]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.92 [3.12, 4.73]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Koyama et al. 2010	RE: 5.04 [3.58, 6.49]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.74 [2.92, 4.55]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Hastings et al. 2010	RE: 5.09 [3.65, 6.54]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.80 [3.00, 4.61]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Oldenburg et al. 2011	RE: 5.60 [3.91, 7.29]	<0.00001	RE: 1.00 [0.97, 1.04]	0.79
	FE: 3.90 [3.02, 4.79]	<0.00001	FE: 1.01 [0.96, 1.05]	0.78
Koyama et al. 2011	RE: 5.21 [3.67, 6.75]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.70 [2.87, 4.53]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Haruki et al. 2011	RE: 5.23 [3.71, 6.74]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.82 [3.01, 4.63]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95
Yoshihisa et al. 2011	RE: 5.33 [3.79, 6.88]	<0.00001	RE: 1.00 [0.97, 1.03]	0.86
	FE: 3.84 [3.03, 4.65]	<0.00001	FE: 1.00 [0.96, 1.04]	0.87
Joho et al. 2012	RE: 4.95 [3.52, 6.38]	<0.00001	RE: 1.00 [0.97, 1.03]	0.98
	FE: 3.69 [2.87, 4.50]	<0.00001	FE: 1.00 [0.96, 1.04]	0.95

LVEF: left ventricular ejection fraction; MD: mean difference; RR: risk ratio; RE: random effect model; FE: fixed effect model.

with chronic heart failure according to analysis of adverse events (including refractory heart failure and worsening heart failure, cardiac arrest, and angina and acute myocardial infarction), with good homogeneity among all these analyses.

Despite the aforementioned results, the impact of NPPV on overall mortality and cardiac adverse events remains to be further investigated. The longest follow-up period among the 19 studies was only 12 months and the shortest was 4 weeks. In a single center cohort study in Canada, patients with OSA were followed up for a decade; however, the study unfortunately did not provide information on cPAP use [50]. In a recent study (which was not included in the present analysis because of the lack of LVEF data), ASV increased the overall and cardiovascular mortality in CHF patients with

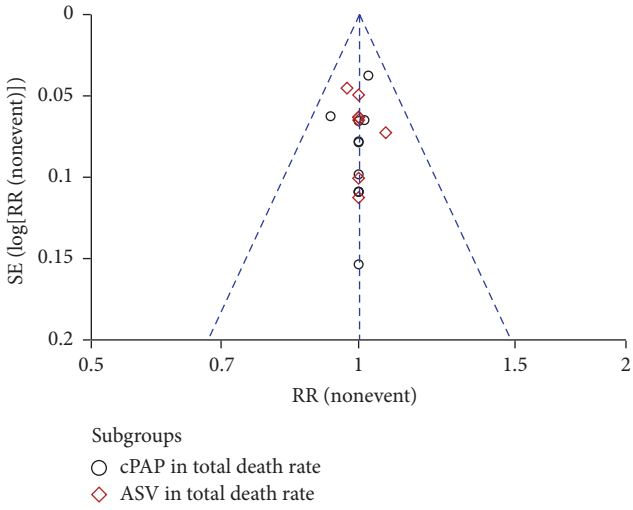


Figure 6: Funnel plot of NPPV on total mortality.

OSA [51]. Thus, more studies are warranted to evaluate the effect of NPPV on 3-year, 5-year, and even 10-year mortality rate.

4.2. Other Secondary Outcomes

4.2.1. NPPV Did Not Reduce LVEDD, but Results of Subgroup Analyses Differed. Five studies reported changes in LVEDD. The present analysis showed that NPPV did not reduce LVEDD; however, heterogeneity was significant. Subgroup analysis, however, yielded a different result. The weighted mean difference was 0.45 favoring (not significantly) control ($P = 0.89$) in the cPAP subgroup, while it was −3.60 favoring ASV ($P = 0.0008$) in the ASV subgroup, indicating that ASV might do better in reducing LVEDD than cPAP, although there was no direct comparison between cPAP and ASV. Further studies are warranted on LVEDD according to NPPV modality.

4.2.2. NPPV Reduces Plasma BNP Level in Patients with Chronic Heart Failure. Among included studies, 6 reported the plasma BNP level at baseline and after intervention. One study focuses on cPAP, while the other five studies focus on ASV. The present analysis showed that the use of NPPV reduced plasma BNP level in CHF patients. Because BNP level can be used to indicate prognosis and predict mortality and clinical outcome of patients with chronic heart failure [33, 52], the reduced BNP level may indicate a better prognosis. However, the subgroup analysis showed no significant difference between cPAP and SMT in influencing plasma BNP level. Since there is only one cPAP study involved, the conclusion may be not applicable to cPAP. Conversely, ASV showed effectiveness in reducing BNP level, possibly indicating that ASV might improve the clinical outcome of CHF patients and reduce mortality. However, the heterogeneity of the analysis was very significant, and further studies are therefore warranted.

ASV was designed to meet the patients' ventilation support by providing inspiratory positive airway pressure (IPAP) and adjust the rate of change of airflow through sensing the patient airflow. cPAP, however, provided a continuous pressure which could not be adjusted according to the patients breath [53]. Several studies showed ASV was associated with significantly better compliance when compared with cPAP [49]. Interestingly, ASV was found to increase 1-year survival rate and reduce cardiovascular events in CHF patient, while cPAP did not show survival benefit among patients with CSA [37].

4.3. Study Limitations. Our study has several potential limitations. First, the sample sizes of component trials included in our analysis are generally not large, which may bring "small-study effects." "Small-study effects" refer to the fact that trials with limited sample sizes are more likely to report larger beneficial effects than large trials [54, 55]. Thus, we performed sensitivity analyses to test the impact of individual trials on the overall result of meta-analysis. Second, only two studies included in our meta-analysis presented the data on NPPV compliance. Ferrier et al. pointed out patients using CPAP (>1 h per night CPAP) had the greatest increase in LVEF [29]; Joho et al. found that the change in average use of ASV correlated with changes in LVEF [41]. However, the definition of NPPV compliance in those reports was not consistent and the influence of compliance to treatment was not quantified. Thus, we did not report the influence of NPPV compliance on studied variables in the present study.

5. Conclusions

In the present meta-analysis, relative to SMT plus sham-NPPV/SMT alone, NPPV plus SMT improved LVEF and reduced plasma BNP level but did not improve overall mortality and adverse event rates.

Abbreviations

NPPV:	Noninvasive positive pressure ventilation
cPAP:	Continuous positive airway pressure
ASV:	Adaptive servoventilation
BiPAP:	Bilevel positive airway pressure
SDB:	Sleep-disordered breathing
OSA:	Obstructive sleep apnea
CSA:	Central sleep apnea
CSR:	Cheyne-Stokes respiration
LVEF:	Left ventricular ejection fraction
LVEDD:	Left ventricular end-diastolic dimension
LVESD:	Left ventricular end-systolic dimension
BNP:	Brain natriuretic peptide
Peak VO_2:	Peak oxygen consumption.

Competing Interests

The authors have no financial disclosures or competing interests to declare.

Authors' Contributions

Hao Jiang and Yi Han contributed equally to this work.

Acknowledgments

This work was supported by the National Science Fund for Distinguished Young Scholars (81625002 to Jun Pu), Program for New Century Excellent Talents of Ministry of Education of China (NCET-12-0352), Shanghai Shuguang Program (12SG22), Program of Shanghai Committee of Science and Technology (15411963600 and 14JC1404500), Shanghai Municipal Education Commission Gaofeng Clinical Medicine Grant Support (20152209), Shanghai Jiaotong University (YG2013MS420), and Shanghai Jiao Tong University School of Medicine (15ZH1003 and 14XJ10019).

References

[1] A. S. Go, D. Mozaffarian, V. L. Roger et al., "Heart disease and stroke statistics—2014 update: a report from the American Heart Association," *Circulation*, vol. 129, no. 3, pp. e28–e292, 2014.

[2] V. L. Roger, S. A. Weston, M. M. Redfield et al., "Trends in heart failure incidence and survival in a community-based population," *The Journal of the American Medical Association*, vol. 292, no. 3, pp. 344–350, 2004.

[3] D. Levy, S. Kenchaiah, M. G. Larson et al., "Long-term trends in the incidence of and survival with heart failure," *The New England Journal of Medicine*, vol. 347, no. 18, pp. 1397–1402, 2002.

[4] F. Simko, K. R. Bednarova, K. Krajcirovicova et al., "Melatonin reduces cardiac remodeling and improves survival in rats with isoproterenol-induced heart failure," *Journal of Pineal Research*, vol. 57, no. 2, pp. 177–184, 2014.

[5] P. A. Heidenreich, N. M. Albert, L. A. Allen et al., "Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association," *Circulation: Heart Failure*, vol. 6, no. 3, pp. 606–619, 2013.

[6] S. Javaheri, T. J. Parker, L. Wexler et al., "Occult sleep-disordered breathing in stable congestive heart failure," *Annals of Internal Medicine*, vol. 122, no. 7, pp. 487–492, 1995.

[7] D. D. Sin, F. Fitzgerald, J. D. Parker, G. Newton, J. S. Floras, and T. D. Bradley, "Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure," *American Journal of Respiratory and Critical Care Medicine*, vol. 160, no. 4, pp. 1101–1106, 1999.

[8] M. Christ, Y. Sharkova, H. Fenske et al., "Brain natriuretic peptide for prediction of Cheyne-Stokes respiration in heart failure patients," *International Journal of Cardiology*, vol. 116, no. 1, pp. 62–69, 2007.

[9] H.-M. Yeung, M.-W. Hung, C.-F. Lau, and M.-L. Fung, "Cardioprotective effects of melatonin against myocardial injuries induced by chronic intermittent hypoxia in rats," *Journal of Pineal Research*, vol. 58, no. 1, pp. 12–25, 2015.

[10] Y. Yang, Y. Sun, W. Yi et al., "A review of melatonin as a suitable antioxidant against myocardial ischemia-reperfusion injury and clinical heart diseases," *Journal of Pineal Research*, vol. 57, no. 4, pp. 357–366, 2014.

[11] L. Yu, H. Liang, X. Dong et al., "Reduced silent information regulator 1 signaling exacerbates myocardial ischemia-reperfusion injury in type 2 diabetic rats and the protective effect of melatonin," *Journal of Pineal Research*, vol. 59, no. 3, pp. 376–390, 2015.

[12] L. Yu, Y. Sun, L. Cheng et al., "Melatonin receptor-mediated protection against myocardial ischemia/reperfusion injury: role of SIRT1," *Journal of Pineal Research*, vol. 57, no. 2, pp. 228–238, 2014.

[13] X. Zhu, J. Fang, D.-S. Jiang et al., "Exacerbating pressure overload-induced cardiac hypertrophy: novel role of adaptor molecule src homology 2-B3," *Hypertension*, vol. 66, no. 3, pp. 571–581, 2015.

[14] L. Gao, K. Huang, D.-S. Jiang et al., "Novel role for caspase-activated DNase in the regulation of pathological cardiac hypertrophy," *Hypertension*, vol. 65, no. 4, pp. 871–881, 2015.

[15] R. Gogiraju, X. Xu, M. L. Bochenek et al., "Endothelial p53 deletion improves angiogenesis and prevents cardiac fibrosis and heart failure induced by pressure overload in mice," *Journal of the American Heart Association*, vol. 4, no. 2, Article ID e001770, 2015.

[16] T. D. Bradley and J. S. Floras, "Sleep apnea and heart failure: part I: obstructive sleep apnea," *Circulation*, vol. 107, no. 12, pp. 1671–1678, 2003.

[17] T. D. Bradley and J. S. Floras, "Sleep apnea and heart failure: part II: central sleep apnea," *Circulation*, vol. 107, no. 13, pp. 1822–1826, 2003.

[18] M. T. Naughton, D. C. Benard, P. P. Liu, R. Rutherford, F. Rankin, and T. D. Bradley, "Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea," *American Journal of Respiratory and Critical Care Medicine*, vol. 152, no. 2, pp. 473–479, 1995.

[19] M. T. Naughton, P. P. Liu, D. C. Benard, R. S. Goldstein, and T. D. Bradley, "Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure," *American Journal of Respiratory and Critical Care Medicine*, vol. 151, no. 1, pp. 92–97, 1995.

[20] Y. Kaneko, J. S. Floras, K. Usui et al., "Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea," *The New England Journal of Medicine*, vol. 348, no. 13, pp. 1233–1241, 2003.

[21] K. Usui, T. D. Bradley, J. Spaak et al., "Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure," *Journal of the American College of Cardiology*, vol. 45, no. 12, pp. 2008–2011, 2005.

[22] T. Kasai, K. Narui, T. Dohi et al., "First experience of using new adaptive servo-ventilation device for Cheyne-Stokes respiration with central sleep apnea among Japanese patients with congestive heart failure—report of 4 clinical cases," *Circulation Journal*, vol. 70, no. 9, pp. 1148–1154, 2006.

[23] M. Arzt, R. Wensel, S. Montalvan et al., "Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure," *Chest*, vol. 134, no. 1, pp. 61–66, 2008.

[24] W. J. Randerath, W. Galetke, S. Stieglitz, C. Laumanns, and T. Schäfer, "Adaptive servo-ventilation in patients with coexisting obstructive sleep apnoea/hypopnoea and Cheyne-Stokes respiration," *Sleep Medicine*, vol. 9, no. 8, pp. 823–830, 2008.

[25] J. C. T. Pepperell, N. A. Maskell, D. R. Jones et al., "A randomized controlled trial of adaptive ventilation for cheyne-stokes breathing in heart failure," *American Journal of Respiratory and Critical Care Medicine*, vol. 168, no. 9, pp. 1109–1114, 2003.

[26] C. Philippe, M. Stoïca-Herman, X. Drouot et al., "Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period," *Heart*, vol. 92, no. 3, pp. 337–342, 2006.

[27] O. Oldenburg, A. Schmidt, B. Lamp et al., "Adaptive servoventilation improves cardiac function in patients with chronic heart failure and Cheyne-Stokes respiration," *European Journal of Heart Failure*, vol. 10, no. 6, pp. 581–586, 2008.

[28] C. J. Egea, F. Aizpuru, J. A. Pinto et al., "Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: a multicenter study," *Sleep Medicine*, vol. 9, no. 6, pp. 660–666, 2008.

[29] K. A. Ferrier, A. M. Neill, T. O'Meeghan, M. Richards, and A. J. Campbell, "Continuous positive airway pressure in heart failure patients with obstructive sleep apnoea," *Internal Medicine Journal*, vol. 38, no. 11, pp. 829–836, 2008.

[30] P. C. Hastings, A. Vazir, G. E. Meadows et al., "Adaptive servoventilation in heart failure patients with sleep apnea: a real world study," *International Journal of Cardiology*, vol. 139, no. 1, pp. 17–24, 2010.

[31] K. G. Johnson and D. C. Johnson, "Bilevel positive airway pressure worsens central apneas during sleep," *Chest*, vol. 128, no. 4, pp. 2141–2150, 2005.

[32] J. P. T. Higgins and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions*, John Wiley & Sons, 2008.

[33] M. Weber and C. Hamm, "Role of B-type natriuretic peptide (BNP) and NT-PROBNP in clinical routine," *Heart*, vol. 92, no. 6, pp. 843–849, 2006.

[34] L. A. Smith, M. Vennelle, R. S. Gardner et al., "Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial," *European Heart Journal*, vol. 28, no. 10, pp. 1221–1227, 2007.

[35] X.-L. Zhang, K.-S. Yin, X.-L. Li, E.-Z. Jia, and M. Su, "Efficacy of adaptive servoventilation in patients with congestive heart failure and Cheyne-Stokes respiration," *Chinese Medical Journal*, vol. 119, no. 8, pp. 622–627, 2006.

[36] M. P. Gilman, J. S. Floras, K. Usui, Y. Kaneko, R. S. T. Leung, and T. D. Bradley, "Continuous positive airway pressure increases heart rate variability in heart failure patients with obstructive sleep apnoea," *Clinical Science*, vol. 114, no. 3, pp. 243–249, 2008.

[37] T. D. Bradley, A. G. Logan, R. J. Kimoff et al., "Continuous positive airway pressure for central sleep apnea and heart failure," *The New England Journal of Medicine*, vol. 353, no. 19, pp. 2025–2033, 2005.

[38] T. Koyama, H. Watanabe, S. Terada et al., "Adaptive servo-ventilation improves renal function in patients with heart failure," *Respiratory Medicine*, vol. 105, no. 12, pp. 1946–1953, 2011.

[39] J. T. Granton, M. T. Naughton, D. C. Benard, P. P. Liu, R. S. Goldstein, and T. D. Bradley, "CPAP improves inspiratory muscle strength in patients with heart failure and central sleep apnea," *American Journal of Respiratory and Critical Care Medicine*, vol. 153, no. 1, pp. 277–282, 1996.

[40] N. Haruki, M. Takeuchi, K. Kaku et al., "Comparison of acute and chronic impact of adaptive servo-ventilation on left chamber geometry and function in patients with chronic heart failure," *European Journal of Heart Failure*, vol. 13, no. 10, pp. 1140–1146, 2011.

[41] S. Joho, Y. Oda, R. Ushijima, T. Hirai, and H. Inoue, "Effect of adaptive servoventilation on muscle sympathetic nerve activity in patients with chronic heart failure and central sleep apnea," *Journal of Cardiac Failure*, vol. 18, no. 10, pp. 769–775, 2012.

[42] T. Koyama, H. Watanabe, Y. Kobukai et al., "Beneficial effects of adaptive servo ventilation in patients with chronic heart failure," *Circulation Journal*, vol. 74, no. 10, pp. 2118–2124, 2010.

[43] O. Oldenburg, T. Bitter, R. Lehmann et al., "Adaptive servoventilation improves cardiac function and respiratory stability," *Clinical Research in Cardiology*, vol. 100, no. 2, pp. 107–115, 2011.

[44] R. Tkacova, P. P. Liu, M. T. Naughton, and T. D. Bradley, "Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure," *Journal of the American College of Cardiology*, vol. 30, no. 3, pp. 739–745, 1997.

[45] A. Yoshihisa, T. Shimizu, T. Owada et al., "Adaptive servo ventilation improves cardiac dysfunction and prognosis in chronic heart failure patients with cheyne-stokes respiration," *International Heart Journal*, vol. 52, no. 4, pp. 218–223, 2011.

[46] M. Arzt, M. Schulz, R. Wensel et al., "Nocturnal continuous positive airway pressure improves ventilatory efficiency during exercise in patients with chronic heart failure," *Chest*, vol. 127, no. 3, pp. 794–802, 2005.

[47] C. B. Johnson, R. S. Beanlands, K. Yoshinaga et al., "Acute and chronic effects of continuous positive airway pressure therapy on left ventricular systolic and diastolic function in patients with obstructive sleep apnea and congestive heart failure," *The Canadian Journal of Cardiology*, vol. 24, no. 9, pp. 697–704, 2008.

[48] D. R. Mansfield, N. C. Gollogly, D. M. Kaye, M. Richardson, P. Bergin, and M. T. Naughton, "Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure," *American Journal of Respiratory and Critical Care Medicine*, vol. 169, no. 3, pp. 361–366, 2004.

[49] T. Kasai, S. Kasagi, K.-I. Maeno et al., "Adaptive servo-ventilation in cardiac function and neurohormonal status in patients with heart failure and central sleep apnea nonresponsive to continuous positive airway pressure," *JACC: Heart Failure*, vol. 1, no. 1, pp. 58–63, 2013.

[50] T. Kendzerska, A. S. Gershon, G. Hawker, R. S. Leung, and G. Tomlinson, "Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study," *PLoS Medicine*, vol. 11, no. 2, Article ID e1001599, 2014.

[51] M. R. Cowie, H. Woehrle, K. Wegscheider et al., "Adaptive servo-ventilation for central sleep apnea in systolic heart failure," *The New England Journal of Medicine*, vol. 373, no. 12, pp. 1095–1105, 2015.

[52] R. Valle, N. Aspromonte, E. Carbonieri et al., "Fall in readmission rate for heart failure after implementation of B-type natriuretic peptide testing for discharge decision: a retrospective study," *International Journal of Cardiology*, vol. 126, no. 3, pp. 400–406, 2008.

[53] H. Teschler, J. Döhring, Y.-M. Wang, and M. Berthon-Jones, "Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 4, pp. 614–619, 2001.

[54] A. Finckh and M. R. Tramèr, "Osteoarthritis: small studies overestimate the benefit of therapies for OA," *Nature Reviews Rheumatology*, vol. 6, no. 11, pp. 617–618, 2010.

[55] Z. Zhang, X. Xu, and H. Ni, "Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study," *Critical Care*, vol. 17, article R2, 2013.