Preoperative FeNO as a screening indicator of pulmonary complications after abdominal surgery in patients over 60 years old

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Abstract
The incidence of pulmonary complications after abdominal surgery is higher than that of cardiac complications. The perioperative factors currently used to assess the risk of postoperative pulmonary complications (PPCs) are imperfect. FeNO is a marker of respiratory system disease related to the airway inflammatory response and bronchial hyperresponsiveness; it may be a new indicator to screen PPCs. A total of 162 patients over 60 years old scheduled for major abdominal surgery under general anesthesia were chosen to measure their preoperative FeNO level. Statistical analyses including the receiver operating characteristic (ROC) and general linear regression were used to analyze the relationships of FeNO with PPCs and other parameters. The medians and quartiles of preoperative FeNO were 14.33 (9.67–21.10) ppb; the geometric mean was 14.25 ppb. Preoperative FeNO were 14.33 (9.67–20.00); the geometric mean was 14.25 ppb. Preoperative FeNO correlated to age (P < 0.05), and the coefficient of association was 0.267. ROC curve analysis of FeNO and PPCs resulted in a high probability with an area under the curve of 0.747 (P = 0.001, 95% confidence interval = 0.602–0.893). The cut-off level was 30.2 ppb, with 47.06% sensitivity and 95% confidence interval of 0.602–0.893. The positive predictive value of the cut-off was 42.11% and negative predictive value was 93.70%. OR value was 10.83. The magnitude of FeNO in the PPCs group was larger than that in the non-PPCs groups 26.20 (11.55–39.20) versus 13.50 (9.55–20.00); (P = 0.008). Preoperative FeNO levels may be used to screen the patients over 60 years old undergoing abdominal surgery with a lower probability to suffer PPCs whose FeNO values less than 30.2 ppb.

1. Introduction
The incidence of pulmonary complications after abdominal surgery is higher than that of cardiac complications and is associated with a prolonged hospital stay [1]. Finlay et al identified four variables that were associated with an increased risk of postoperative pulmonary complications (PPCs): age, positive cough test, perioperative nasogastric tube and the duration of anesthesia [2]. PPCs, including pneumonia, bronchitis, pulmonary atelectasis, respiratory insufficiency, in patients over 60 years old undergoing abdominal surgery with general anesthesia occur more frequently than PPCs in other patients. The occurrence of these complications has a strong impact on prognosis and increased costs of care, and they are also one of the major causes of death during the perioperative period in patients over 60 years of age. The ability to identify which patients are at high risk for PPCs may contribute to assigning patients for surgical intervention, informing patients about perioperative risks, making plans to reduce risk, and allocating resources for postoperative care [3]. However, as far as we know the perioperative factors that are currently used to assess the risk of PPCs are imperfect [4].

Nitric oxide within the lungs comes from differing sources, such as the bronchial epithelium, alveolar cells, vascular endothelium and lung interstitial macrophages [5]. It is also produced by epithelial cells, vascular endothelial cells, inflammatory cells and others. Since Gustafsson et al [6] reported the measurable levels of fractional exhaled nitric oxide (FeNO) in
humans, it has become a marker of respiratory system disease that is applicable to the airway inflammatory response and bronchial hyperresponsiveness. Dweik et al pointed out that when the symptoms presented during past 6 weeks and the level of FeNO was higher than 50 parts per billion (ppb), the patients could be diagnosis as eosinophilic airway inflammation in an official ATS clinical practice guideline [7]. However, the FeNO levels in some infectious diseases such as community acquired pneumonia, bronchiectasis, viral pulmonary infections are still controversial [8]. At present, it has been postulated that FeNO may be a useful and cost-effective component of a large population screening project for the diagnosis of asthma [9]. Jo et al reported the optimal cut-off values for the prediction of asthma in the healthy Korean elderly population were 30.5 ppb for males and 20.5 ppb for females [10]. Park et al found that FeNO may be useful for monitoring the parenchymal inflammation of chronic eosinophilic pneumonia [11]. The magnitude of FeNO increases along with bronchial wall inflammation [12]. Therefore, FeNO may be used as a noninvasive biomarker of respiratory inflammation in the clinic.

Based on the role of FeNO in the airway inflammatory response, we speculated that FeNO might be a new indicator to screen PPCs. In this study, we chose 162 patients over 60 years old who were undergoing abdominal surgery with general anesthesia. We measured the preoperative FeNO of these patients and also recorded data from the perioperative period to analyze the relationship between FeNO and PPCs.

2. Methods

The prospective study was approved by the ethics committee of Harbin Medical University (no. 201314), and written informed consent was obtained from the patients prior to study enrollment. Patients over 60 years old who were scheduled for major abdominal surgery under general anesthesia in our regional university hospital—the 1st Affiliated Hospital of Harbin Medical University, China—between March 2013 and December 2014 were eligible.

2.1. Patients

Patients who met the following conditions were included: (1) their age was at least 60 years old; (2) they were scheduled to undergo elective major abdominal surgery under general anesthesia with mechanical ventilation; and (3) they did not have other serious systemic complications except for complications of the digestive system. Patients were rejected due to the following conditions: (1) their body mass index (BMI) was greater than 35 kg m⁻²; (2) they were receiving or had received corticosteroid therapy in one year; (3) they were experiencing the acute stage of respiratory system disease before surgery; (4) their surgery was an emergency; (5) their hemodynamic stability was not persistent; and (6) they had any neuromuscular diseases or psychosis. The preoperative characteristics of patients and all analyzed parameters are demonstrated in table 1.

2.2. Anesthesia procedures

After patients entered the operation room, electrocardiography, pulse oxygen saturation (SPO₂), invasive arterial pressure (measured every 5 min) and bispectral index (BIS) were monitored (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland). All of the patients received routine anesthesia according to an established protocol that included intravenous propofol (1–2 mg kg⁻¹), sufentanil (0.25–0.5 μg kg⁻¹) and 0.2 mg kg⁻¹ cis-atracurium before intubation. Anesthesia was maintained with sevoflurane (end tidal concentration ≥0.7 MAC) to maintain a BIS index of 40–60, cis-atracurium (0.05 mg kg⁻¹) was intermittently applied every 40 min for the duration of the operation. The ventilation protocol was: 6–8 ml kg⁻¹ ideal body weight and 8 cm H₂O positive end expiratory pressure (PEEP) (Drager Fabius GS premium; Drager Medical AG, Lubeck, Germany), recruitment maneuvers (RMs) was implemented just after intubation and repeated every 30 min; an inspiratory to expiratory ratio of 1:2; FiO₂ maintained at approximately 0.3; and the end-tidal carbon dioxide partial pressure (PetCO₂) was kept between 30 and 40 mmHg.

Table 1. Characteristics of patients.

| Variables analyzed | Mean ± SD / median [IQR] |
|--------------------|--------------------------|
| Age (years)        | 66.00(63.00–71.00)        |
| Gender (male; %)   | 100(61.73)                |
| Body height (cm)   | 164.66 ± 7.65             |
| Body weight (kg)   | 62.21 ± 11.18             |
| BMII(kg/m²)        | 2.29 ± 3.52               |
| Left ventricle ejection fraction (%) | 61.5 ± 2.2 |
| Coexisting condition, n(%) |                     |
| History of smoking | 48(29.63)                |
| Chronic obstructive pulmonary disease | 14(8.64) |
| Asthma             | 2(1.23)                  |
| Type of surgery, n(%) |                              |
| Non-laparoscope surgery | 118(72.84)           |
| Gastrectomy        | 35(29.67)                |
| Pancreatectoduodenectomy | 10(8.47) |
| Colorectal resection | 61(51.69)       |
| Other procedure    | 12(10.17)                |
| Laparoscope surgery | 44(27.16)                |
| Colorectal resection | 39(88.63)       |
| Other procedure    | 5(11.36)                 |
| Classification of PPCs, n(%) |              |
| Dyspnea            | 14(82.35)                |
| Pneumonia          | 17(100)                  |
| Pneumothorax       | 0                        |
| Respiratory distress | 3(17.64)         |
| Chronic respiratory failure | 2(11.76)   |
2.3. Data measurement and follow-up
FeNO was significantly influenced by various short-term factors such as diet, smoking, strenuous exercise and environmental exposure. Patients scheduled to undergo surgery in the hospital fasted at least 4 h, refrained from smoking for at least 72 h, rested in bed and breathed purified air for several days. A nitric oxide analyzer (NIOX; Aerocrine, Solna, Sweden) was used to standardize FeNO prior to anesthesia for 10 min according to the guidelines of the American Thoracic Society/European Respiratory Society. After a simple demonstration of the procedure, patients were asked to exhale as much air as they could and then inhaled NO-free air to total lung capacity. The patients then closed the velopharyngeal aperture to eliminate interference of NO from the nose. Next, the patients were instructed to exhale accurately at a constant rate of 50 ml s$^{-1}$ through a filter for 10 s.

After FeNO measurements were taken, forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) values were immediately obtained at the bedside using a portable spirometer (Master-Screen GE, Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA). The patient sat vertically at the bedside and breathed by mouth though the filter while simultaneously pinching their nose. Then, the patient was asked to inhale as deeply and exhale as forcefully and quickly as possible. We repeated the process 3 times to ensure that we acquired the highest value.

Routine intraoperative monitoring included dynamic pressure-volume curve; infusion volume; bleeding volume; urine volume and blood transfusion. The patients were observed postoperatively for the following: PPCs including dyspnea, pneumonia, pneumothorax, respiratory distress and chronic respiratory failure that were diagnosed by the pulmonology department or the ICU attending physicians; acute heart failure; primary postoperative intensive care unit (ICU) admission; duration of hospitalization; and in-hospital death.

2.4. Statistical analysis
The data are presented as the means ± standard deviation (SD) for normal distribution, medians and quartiles for skewed distribution and percentages on an intention-to-treat basis. FeNO values are described as the median and geometric mean. The relationships between FeNO and all indexes were assessed with correlation analysis. Receiver operating characteristic (ROC) curve analysis was used to estimate the sensitivity and specificity of FeNO in screening PPCs. The data were analyzed using the independent-samples t test, non-parametric test or chi-square test. Statistical significance was set at $p < 0.05$. Based on the effective rate was 10% in preliminary experiment, the sample size was 78 ($\alpha = 0.05, \beta = 0.10$). All of the statistical analyses were performed with SPSS software, version 16.0.

3. Results
856 consecutive patients, who were scheduled to undergo the major abdominal surgery, were screened. Most of them had exclusion criteria, leaving 172 patients enrolled. However, 10 of them were unable to accomplish the measurement of FeNO, 162 patients participated in this study in the end (figure 1). The medians and quartiles of FeNO values were 14.33 (9.67–21.10) ppb, and the geometric mean was 14.25 ppb in preoperative patients over 60 years. Table 2 shows the distribution of FeNO values. The main distribution areas were 1–10 ppb, 10–20 ppb and 20–30 ppb, and the proportions were 27.16%, 45.68% and 15.43%, respectively. Preoperative FeNO values correlated
to the patients’ age; the coefficient of association was 0.267 ($p < 0.05$). Preoperative FeNO values had no correlation with other characteristics including sex, height, weight, BMI, preoperative FEV1 and FVC in our data. Table 3 showed the levels of FeNO had no difference in different types of surgery ($p = 0.88$). The ROC curve analysis of the correlation between FeNO values (figure 2) and PPCs resulted in a high probability with an area under the curve of 0.747 ($p = 0.001$; 95% confidence interval =0.662–0.893). The cut-off FeNO value of 30.2 ppb had the best combination of sensitivity (47%) and specificity (93%). The positive predictive value of the cutoff was 42.11% and negative predictive value was 93.70%. OR value was 10.83.

Table 2. Distribution of FeNO in preoperative elderly patients.

| Magnitude | Number | Percentage (%) | Medians and quartiles (ppb) | Geometric mean (ppb) |
|-----------|--------|----------------|-----------------------------|----------------------|
| 0–10 ppb  | 44     | 27.16          | 7.70(5.75–9.00)             | 6.82                 |
| 10–20 ppb | 74     | 45.68          | 14.25(11.75–17.05)          | 14.19                |
| 20–30 ppb | 25     | 15.43          | 24.1(21.60–26.95)           | 24.09                |
| 30–40 ppb | 14     | 8.64           | 35.70(31.38–38.43)          | 34.82                |
| 40–50 ppb | 1      | 0.62           | 43.90                       | 43.90                |
| 50–60 ppb | 2      | 1.23           | 54.30                       | 54.19                |
| 60–70 ppb | 2      | 1.23           | 67.45                       | 67.41                |

Table 3. The Levels of FeNO before different operations

| Type of surgery                  | FeNO (ppb)          | $P$ value |
|----------------------------------|---------------------|-----------|
| Gastrectomy ($n = 28$)           | 15.30(9.63–29.35)   | 0.88      |
| Pancreatoduodenectomy ($n = 12$) | 14.45(8.28–22.60)   | 0.88      |
| Colorectal resection ($n = 58$)  | 14.10(10.03–20.63)  |           |
| Other procedure ($n = 64$)       | 14.00(9.35–20.18)   |           |

Figure 2. The ROC curve analysis of FeNO, the area under the curve is 0.747.

Compared with the non-PPCs group, the FeNO level in PPCs group was higher 26.20 (11.55–39.20) ppb versus 13.50 (9.55–20.00) ppb; $p = 0.008$), and results show that laparoscopic surgery could influence the occurrence of PPCs (1(5.88%) versus 43(29.66%); $p = 0.043$). There were no differences between the PPCs and non-PPCs group in age, gender, pulmonary function, the duration of ventilation and operation, and the vast majority of intraoperative data (table 4).

4. Discussion

This study shows that FeNO levels in preoperative patients over 60 years old who were scheduled for major
abdominal surgery range from 5.05 ppb (5th percentile) to 38.48 ppb (95th percentile), with a geometric mean of 14.25 ppb. To our knowledge, this study is the first prospective study to assess the relationship between FeNO and PPCs by showing the distribution and cutoff level of FeNO when screening for PPCs. Measuring FeNO just before anesthesia may be a useful and cost-effective component of large population screening project for patients over 60 years old who are undergoing surgery with general anesthesia. FeNO values for healthy children were associated with height [13], whereas FeNO values for healthy adults were associated with age and height [14]. In our study, it seems that age may be a unique factor that could not be influenced by preoperative pathophysiological status in terms of its effect on FeNO. FeNO comes from a bolus of air which traverses the alveolar region through the airways. The lung-diffusing transfer factors for NO/alveolar volume were age dependent with a progressive decrease after age 59 years [15]. Gelb et al [16] pointed out the reasons for the increased FeNO with age ≥60 years may be an increase in NO tissue production as an up-regulation (increased NO synthase) or inflammatory response and the reduced diffusing capacity of NO.

FeNO is influenced by a variety of factors, such as corticosteroid therapy, cardiac insufficiency and the acute stage of respiratory disease. We standardized the patients with respect to these factors according to the inclusion and exclusion criteria used in this study. Ventilation strategy can also impact the incidence of PPCs [17]. We standardized the ventilation strategy with low tidal volume PEEP and RMs. In this study, we chose patients who were scheduled for major abdominal surgery and were already at high risk for PPCs due to their age being greater than 60 years, the use of a perioperative nasogastric tube, and the long duration of general anesthesia used during surgery. Preoperative FeNO values became a new screening guideline for these high-risk patients compared with the traditional screening mode. FeNO levels may be used to screen the patients with a lower probability to suffer PPCs whose FeNO values less than 30.2 ppb.

| Variables analyzed                      | PPCs (n = 17)       | non-PPCs (n = 145) | P value |
|----------------------------------------|---------------------|--------------------|---------|
| Preoperation                            |                     |                    |         |
| FeNO (ppb)                             | 26.20(11.55–39.20)  | 13.50(9.55–20.00)  | 0.008   |
| Age (years)                            | 65.00(61.50–67.50)  | 66(62.5–71.00)     | 0.15    |
| Gender (male; n(%))                    | 13(76.47%)          | 87(60.00%)         | 0.14    |
| FEV1 (L)                               | 2.52(1.61–2.95)     | 2.17(1.70–2.75)    | 0.19    |
| FVC (L)                                | 2.88 ± 0.89         | 2.48 ± 0.28        | 0.07    |
| Introparation                           |                     |                    |         |
| Laparoscope surgery n(%)               | 1(5.88%)            | 43(29.66%)         | 0.04    |
| Duration of ventilation (h)            | 3.30(1.94–3.98)     | 2.95(2.00–3.50)    | 0.63    |
| Duration of operation (h)              | 2.50(1.50–3.25)     | 2.47(1.50–3.00)    | 0.99    |
| Base                                   |                     |                    |         |
| Systolic pressure (mmHg)               | 149.63 ± 25.67      | 137.38 ± 13.13     | 0.19    |
| Diastolic pressure (mmHg)              | 79.77 ± 13.72       | 81.13 ± 4.70       | 0.78    |
| Heart rate (bpm)                       | 77.36 ± 12.77       | 76.00 ± 9.49       | 0.78    |
| SpO2 (%)                               | 97.20(95.50–98.50)  | 97.50(94.25–98.75) | 0.60    |
| PauCO2 (mmHg)                          | 32(30–34)           | 32(30–34.5)        | 0.78    |
| Respiratory system compliance (L/cmH2O)| 56(42–69)           | 43(34–57)          | 0.07    |
| End                                     |                     |                    |         |
| Systolic pressure (mmHg)               | 135(116–160) 71.66 ± | 111(105.50–135.50)| 0.03    |
| Diastolic pressure (mmHg)              | 13.36               | 69.50 ± 9.94       | 0.54    |
| Heart rate (bpm)                       | 80(69–87.75)        | 79.50(75.5–93.75)  | 0.70    |
| SpO2 (%)                               | 95.5(92.5–98)       | 94(91.50–97.75)    | 0.53    |
| PauCO2 (mmHg)                          | 33(31–34)           | 33(33–33.75)       | 0.17    |
| Respiratory system compliance (L/cmH2O)| 54.35 ± 15.76      | 53.30 ± 15.77      | 0.07    |
| Infusion volume (L)                    | 2.00(1.50–2.50)     | 1.50(1.00–2.00)    | 0.02    |
| Bleeding volume (ml)                   | 100(35–200)         | 30 (5–50)          | 0.009   |
| Urine volume (ml)                      | 400(150–650)        | 300(200–600)       | 0.31    |
| Blood transfusion n(%)                 | 3(17.65)            | 16(11.03)          | 0.32    |
| Postoperation                           |                     |                    |         |
| Acute cardiac failure n(%)             | 1(5.88)             | 0                   | 0.12    |
| ICU admission n(%)                     | 14(82.35)           | 6(4.14)            | 0.001   |
| Duration of stay in hospital (d)       | 29.50(17.25–42.00)  | 18.00(15.00–22.50) | 0.001   |
| Death in hospital n(%)                 | 1(5.88)             | 0                   | 0.12    |

Table 4. Data of PPCs and non-PPCs patients.
Nitric oxide (NO) plays a key role in the regulation of vasomotor tone and local blood flow in pulmonary circulation [18]. The lungs themselves continuously generate NO from the amino acid L-arginine via constitutive NO synthases within the pulmonary vascular endothelium and the epithelial lining of the airways under normal conditions [19]. Endothelial cells play a considerable part in the regulation of vascular homeostasis in the lungs. The measurable normal levels of FeNO reflect the capacity of the endothelial cells.

NO is also an important element with levels that correlate with the pathophysiology of microcirculatory mechanisms of the respiratory system [20]. Pathologic NO is synthesized by inducible nitric oxide synthase, which is expressed by inflammatory cells in response to cytokines and bacterial endotoxins. In many inflammatory conditions, the overproduction of pathologic NO is expressed by NO reacting rapidly with reactive oxygen species, leading to NO-metabolites. Healthy patients with high FeNO levels may experience a potential pulmonary inflammatory environment (may not severity to stimulate reactive oxygen species). In our study, the incidence rate of PPCs is greatly decreased when the patient’s preoperative FeNO level is less than 30.2 ppb, with a specificity of 93.1%. The FeNO level of the PPCs group is significantly greater than that of the non-PPCs group. These findings indicate that the patients with an increase of preoperative FeNO may have a more high-risk to suffer PPCs due to the overproduction of pathologic NO responding to the condition of this potential lung inflammation environment.

Laparoscopic surgery was another factor for which a significant difference between the PPCs and non-PPCs patients was demonstrated. Laparoscopic surgery is an important strategy to reduce the rate of PPCs due to its reduced postoperative pain, and its ability to facilitate deep breathing and active coughing [24]. However, the vast majority of intraoperative data showed no difference, which means preoperative assessment is more useful and meaningful for screening for patients who are at high risk for developing PPCs.

While, we still have some limitations. As current smokers, allergic rhinitis or atopy may influence the levels of FeNO, but we didn’t exclude these factors in our study. In our further study, we will improve the guideline to eliminate the disturbances of these factors.

5. Conclusions

Preoperative FeNO may be used to screen the patients over 60 years old undergoing abdominal surgery with a lower probability to suffer PPCs whose FeNO values less than 30.2 ppb.

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Conflict of interest statements

The authors of this manuscript declare there are no conflicts of interest.

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References

[1] Lawrence V A, Hilsenbeck S G, Mulrow C D, Dhanda R, Sapp J and Page C P 1995 Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery J. Gen. Intern. Med. 10 671–9
[2] McAlister F A, Bertsch K, Man J, Bradley J and Jacka M 2005 Incidence of and risk factors for pulmonary complications after nonthoracic surgery Am. J. Respir. Crit. Care Med. 171 514–7
[3] Ferguson M K, Celauro A and Dand Prachand V 2011 Prediction of major pulmonary complications after esophagectomy Ann. Thorac. Surg. 91 1494–500
[4] Fisher B W, Majumdar S R and McAlister F A 2002 Predicting pulmonary complications after nonthoracic surgery: a systematic review of blinded studies Am. J. Med. 112 219–25
[5] Cuthbertson B H, Stott S A and Webster N R 2011 Exhaled nitric oxide as a marker of lung injury in coronary artery bypass surgery Br. J. Anaesth. 89 247–50
[6] Gustafsson L E, Leone A M, Persson M G, Wiklund N P and Moncada S 1991 Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans Biochem. Biophys. Res. Commun. 181 852–7
[7] Dweik R A, Boggs P B, Erzurum S C, Irving C G, Leigh M W, Lundberg JO, Olin A C, Plummer A L and Taylor D R 2011 An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FeNO) for clinical applications Am. J. Respir. Crit. Care Med. 184 602–15

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References

[1] Lawrence V A, Hilsenbeck S G, Mulrow C D, Dhanda R, Sapp J and Page C P 1995 Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery J. Gen. Intern. Med. 10 671–9
[2] McAlister F A, Bertsch K, Man J, Bradley J and Jacka M 2005 Incidence of and risk factors for pulmonary complications after nonthoracic surgery Am. J. Respir. Crit. Care Med. 171 514–7
[3] Ferguson M K, Celauro A and Dand Prachand V 2011 Prediction of major pulmonary complications after esophagectomy Ann. Thorac. Surg. 91 1494–500
[4] Fisher B W, Majumdar S R and McAlister F A 2002 Predicting pulmonary complications after nonthoracic surgery: a systematic review of blinded studies Am. J. Med. 112 219–25
[5] Cuthbertson B H, Stott S A and Webster N R 2011 Exhaled nitric oxide as a marker of lung injury in coronary artery bypass surgery Br. J. Anaesth. 89 247–50
[6] Gustafsson L E, Leone A M, Persson M G, Wiklund N P and Moncada S 1991 Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans Biochem. Biophys. Res. Commun. 181 852–7
[7] Dweik R A, Boggs P B, Erzurum S C, Irving C G, Leigh M W, Lundberg JO, Olin A C, Plummer A L and Taylor D R 2011 An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FeNO) for clinical applications Am. J. Respir. Crit. Care Med. 184 602–15
[8] Manna A, Caffarelli C, Varini M, Povesi Dascola C, Montella S, Maglione M, Sperli F and Santamaria F 2012 Clinical application of exhaled nitric oxide measurement in pediatric lung diseases Ital. J. Pediatr. 38 74

[9] Kharitonov S A 2004 Exhaled markers of inflammatory lung diseases: ready for routine monitoring? Swiss. Med. Wkly. 134 175–92.

[10] Jo E J et al 2014 Reference ranges and determinant factors for exhaled nitric oxide in a healthy Korean elderly population Allergy Asthma Immunol. Res. 6 504–10.

[11] Park J Y et al 2014 Significance of fractional exhaled nitric oxide in chronic eosinophilic pneumonia: a retrospective cohort study BMC Pulm. Med. 14 61.

[12] Payne D N, Adcock I M, Wilson N M, Oates T, Scallan M and Bush A 2001 Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone Am. J. Respir. Crit. Care Med. 164 1376–81.

[13] Mallol J, Aguirre V, Córdova P, Cortez E, Gallardo A and Riquelme C 2014 Fraction of exhaled nitric oxide in healthy Chilean schoolchildren aged 8–15 years Allergol. Immunopathol. (Madr.) pii S0301-0546(14)00138-4.

[14] Leng G, Li Z and Wang Q 2012 Detection of exhaled nitric oxide of healthy in Nanjing J. Clin. Otorhinolaryngol. Head Neck Surg. (China) 26 769–71.

[15] Verbanck S, Kerckx Y, Schuurmans D, de Bisschop C, Guénaud H, Naeije R, Vincken W and Van Muylen A 1985 The effect of posture-induced changes in peripheral nitric oxide uptake on exhaled nitric oxide J. Appl. Physiol. 106 1494–8.

[16] Gelb A F, George S C, Camacho E, Fraser C, Flynn Taylor C, and Shakhova S 2011 Increased nitric oxide concentrations in the small airway of older normal subjects Chest 139 368–75.

[17] Futier E et al 2013 A trial of intraoperative low-tidal-volume ventilation in abdominal surgery N. Engl. J. Med. 369 428–37.

[18] Dinh-Xuan A T 1992 Endothelial modulation of pulmonary vascular tone Eur. Respir. J. 5 737–62.

[19] Boshier P R, Hanna G B and Marczin N 2013 Exhaled nitric oxide as biomarker of acute lung injury: an unfulfilled promise J. Breath Res. 7 017118.

[20] Wilkins M R, Zhao L and al-Tubuly R 1996 The regulation of pulmonary vascular tone Br. J. Clin. Pharmacol. 42 127–31.

[21] Adrie C, Monchi M, Dinh-Xuan A T, Dall’Ava-Santucci, J, Dhainaut J F and Pinsky M R 2001 Exhaled and nasal nitric oxide as a marker of pneumonia in ventilated patients Am. J. Respir. Crit. Care Med. 163 1143–9.

[22] Neto A S et al 2014 Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis Lancet Respir. Med. 2 1007–15.

[23] Kovess T and Dales R 2008 Exhaled nitric oxide and respiratory symptoms in a community sample of school aged children Pediatr. Pulmonol. 43 1198–205.

[24] Jeong B H et al 2014 Development of a prediction rule for estimating postoperative pulmonary complications PLoS One 9 e113656.