Exhaled acetone and isoprene in perioperative lung cancer patients under intensive oral care: possible indicators of inflammatory responses and metabolic changes

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ABSTRACT
One of the most severe complications of lung resection is postoperative pneumonia, and its prevention and prediction are critical. Exhaled acetone and isoprene are thought to be related to metabolism; however, little is known on their relationship with bacteria living in the oral cavity or their meaning in the acute phase in perioperative lung cancer patients. We measured acetone and isoprene in exhaled breath of 13 Japanese patients with lung cancer (3 women and 10 men, age range 62–82 years, mean 72.4 years) before breakfast during hospitalization, and compared with two acute-phase proteins, C-reactive protein (CRP) and albumin in blood serum, as well as the total number of bacteria in saliva and their activity to produce acetone and isoprene. Before operation, intensive oral care was carried out for each patient to prevent postoperative pneumonia, and swallowing and cough reflexes were measured for 12 of 13 patients to assess risk of postoperative pneumonia. Breath and saliva were sampled before intensive oral care (T1), after oral care but before operation (T2), and after operation (T3) during hospitalization. The total number of oral bacteria in saliva decreased significantly from T1 to T2 among 13 patients. No acetone or isoprene was detected from saliva after in vitro incubation under anaerobic or aerobic conditions, but both acetone and isoprene were detected in breath. After operation, breath acetone correlated significantly with CRP (Spearman’s ρ = 0.559, P = 0.03), but not with albumin. Breath isoprene correlated significantly with albumin (Spearman’s ρ = 0.659, P = 0.008), but not with CRP after operation. Although the number of subjects was small, our results support the hypothesis that breath acetone and isoprene may be related with these acute-phase proteins, which reflect inflammatory reactions and subsequent changes in metabolism in the early postoperative phase of lung resection.

One of the most severe respiratory complications of lung resection is postoperative pneumonia, and its prevention and prediction are critical. Microbial airway colonization is a main step to this complication and some factors, including chemotherapy and oro-pharyngeal microbial flora, are suggested to affect the occurrence of airway colonization (5). Pneumonia in elderly people is mainly caused by silent aspiration due to age-related impairment of cough and swallowing reflexes. As most patients with lung cancer are elderly, the age-related impairment of these protective reflexes may occur in patients undergoing lung surgery, causing postoperative pneu-
monia. We prospectively reported that 30 elderly patients who received perioperative intensive oral care did not develop pneumonia after lung resection (10); however, how oral bacteria or inflammatory responses change and how to evaluate the risk of postoperative pneumonia in the perioperative period remain to be answered.

Breath analysis has been suggested as a noninvasive approach for the early detection of pathological processes during the perioperative period (2, 3). We have reported that exhaled acetone positively correlated with β-hydroxybutyrate and acetacetate in oral glucose tolerance test of healthy Japanese and breath acetone may be related with plasma ketone bodies which reflect the decreased glucose metabolism (26). Kischkel et al. reported that exhaled acetone concentrations increased significantly at post-surgery compared with pre-surgery through lipolysis and ketogenesis after prolonged fasting in perioperative lung cancer (15). In lung cancer patients, isoprene concentration positively correlated with total cholesterol and LDL cholesterol, whereas inverse correlation existed between isoprene and an immune activation marker neopterin (8). Isoprene was also proposed as a potential biomarker for advanced fibrosis in patients with chronic liver disease, although it was not correlated with plasma cholesterol (1).

C-reactive protein (CRP) is widely used as a systemic marker of inflammation, tissue damage, infection, and malignant neoplasia (20). It is considered as an early predictor of infectious postoperative complications in rectal surgery (29), and suggested as an indicator for prognostic significance in patients with advanced cell lung cancer (16) and correlated with albumin in patients with inoperable non-small-cell lung cancer (7). Albumin is considered as a negative acute-phase protein because its concentration in serum decreases during injury and sepsis (25). Albumin levels are influenced by inflammation, confirming it to be a ‘negative acute-phase protein’ in hemodialysis patients (13). It was also suggested as a biomarker of gastrointestinal mucositis in recipients of hematopoietic stem cell transplantation (27). The combination of CRP and albumin has been reported as an independent prognostic value in patients with cancer (17).

In this study, we assessed breath acetone and isoprene in perioperative lung cancer patients who were under intensive oral care for preventing from pneumonia. The aim was to clarify the possible role of acetone and isoprene as early predictors of infectious postoperative complications in lung resection.

MATERIAL AND METHODS

Ethical consideration. The Ethics Committee of Tohoku University Graduate School of Dentistry, Sendai, Japan, approved the study (admittance number 23-17). Written informed consent was obtained from all patients.

Hospitalized patients under oral hygiene program. We studied 13 patients (3 women and 10 men, age range 62–82 years, mean 72.4 years) who were operated on for lung cancer at the Department of Thoracic Surgery of Tohoku University Hospital. Two patients underwent introductory radio-chemotherapy before operation. Seven patients had history of pulmonary diseases in addition to pulmonary tumor. Detailed demographic characteristics are given in Table 1. Routine clinical examinations included serum CRP and albumin measurements in the perioperative period. They received oral examinations, hygiene instructions, supragingival scaling, professional mechanical cleaning of the tooth surfaces and/or dentures, and tongue cleaning as intensive oral care. This was performed at least 2 days prior to surgery at the Department of Preventive Dentistry of Tohoku University Hospital.

Assessment of upper respiratory protective reflexes. Prior to lung resection, one thoracic surgeon measured cough and swallowing reflexes, and evaluated them as previously reported (6, 9, 12). Cough reflex sensitivity was measured using citric acid (Wako Pure Chemical Industries, Osaka, Japan) delivered by an ultrasonic nebulizer (Ultra X UN-703; Alfresa Pharma, Osaka, Japan). Citric acid was administered in incremental concentrations from 2.25% to 36% (two-fold serial dilutions; scores 6–10, respectively). Increasing concentrations were inhaled until three or more coughs had been elicited consecutively; the sensitivity of the cough reflex was scored according to the lowest concentration of citric acid that elicited three or more coughs. Cough reflexes with sensitivity of more than 2.25% (scores > 6) were regarded as impaired. Swallowing reflexes were induced by bolus injection of 1.0 mL distilled water into the pharynx through a nasal catheter. Subjects were unaware of the time of injection. Swallowing was identified by visual observation of characteristic laryngeal movements. The swallowing reflex was quantified as latency time of the swallowing reflex (LTSR) from the injection to the onset of swallowing. Patients were classified into the low-risk group (LTSR < 3.0 s), intermediate-risk group (3.0 s < LTSR < 3.0 s).
< 6.0 s), or high-risk group (LTSR ≥ 6.0 s) (Table 2).

**Acetone and isoprene analysis by Gas Analyzer XG-100V.** We used the Gas Analyzer XG-100V (New Cosmos Electric Co., Ltd., Osaka, Japan), a portable gas chromatograph using an In$_2$O$_3$ thick film-type gas sensor. A detailed description of the XG-100 analytical system has been reported previously (26). The sensor is based on a thick In$_2$O$_3$ film, where Pd and Pt are applied as catalysts to a limited area of the film to promote sensitivity and improve selectivity of the targeted gases. It consists of a sensor cell with a thick highly sensitive In$_2$O$_3$ film, a separation column, an auto-sampling device, a temperature control unit with a heater, a mass flow controller, an air pump, a circuit board with a serial communication interface, a stainless steel air buffer with activated carbon which is also used as an air filter, and a notebook PC with software for data analysis. The air is pumped into the air filter to be cleaned as the carrier gas of the system and the flow rate of the carrier gas is controlled at 20 mL/min by the mass flow controller.

### Table 1  Demographic characteristics of patients

| Patient | Age yrs | Sex | Tumor histology | Surgery | ICRT | Medical history |
|---------|---------|-----|-----------------|---------|------|-----------------|
| P1      | 80      | Male| Squamous cell ca.| Wedge resection | –    | Interstitial pneumonia |
| P2      | 64      | Male| Adenocarcinoma   | Lobectomy | –    | Thyroid cancer |
| P3      | 80      | Female| Adenocarcinoma  | Lobectomy | –    | Lung sarcoïdosis |
| P4      | 69      | Male| Adenocarcinoma   | Lobectomy, Chest wall resection reconstruction | +    | Anemia |
| P5      | 62      | Female| Squamous cell ca.| Lobectomy, lymph node dissection | –    | COPD |
| P6      | 82      | Female| Adenocarcinoma  | Lobectomy | –    | Angina pectoris |
| P7      | 78      | Male| Adenocarcinoma   | Lobectomy | –    | Idiopathic pulmonary fibrosis |
| P8      | 75      | Male| Squamous cell ca.| Lobectomy | –    | Obstructive pneumonia |
| P9      | 68      | Male| Adenocarcinoma   | Lobectomy | –    | Parkinson’s disease |
| P10     | 75      | Male| Renal cell ca., metastatic | Lobectomy, lymph node dissection | –    | Renal carcinoma |
| P11     | 69      | Male| Squamous cell ca.| Lobectomy, lymph node dissection | –    | COPD |
| P12     | 67      | Male| Adenocarcinoma   | Pneumonectomy, lymph node dissection | +    | Chronic emphysema |
| P13     | 72      | Male| Adenocarcinoma   | Lobectomy | –    | Old cerebral infarction |

ICRT: introductory radio-chemotherapy.

### Table 2  Preoperative upper respiratory protective reflexes and perioperative change in CRP, albumin, acetone, and isoprene

| Patient | Cough reflex | Risk grade by LTSR | CRP (mg/dL) | Albumin (g/dL) | Acetone (ppb) | Isoprene (ppb) | CRP (mg/dL) | Albumin (g/dL) | Acetone (ppb) | Isoprene (ppb) |
|---------|--------------|---------------------|-------------|----------------|---------------|----------------|-------------|----------------|---------------|----------------|
| P1      | normal       | intermediate        | 1.2         | 3.6            | 620.4         | 234            | 21.8        | 3.1            | 1317.7        | 202            |
| P2      | normal       | low                 | 0.1         | 4.1            | 484           | 393            | 1.2         | 3.4            | 453           | 331            |
| P3      | normal       | low                 | 0.1         | 3.9            | 826.9         | 136.8          | 3.1         | 3.1            | 657.1         | 293.4          |
| P4      | normal       | high                | 0.3         | 4              | 397.7         | 98.8           | 14.5        | 2.9            | 1492.8        | 303.2          |
| P5      | normal       | low                 | 0.1         | 3.2            | 651.3         | 275.8          | 3.5         | 3.2            | 925.1         | 283            |
| P6      | normal       | low                 | 0.1         | 4.2            | 591           | 293.1          | 16.5        | 3.3            | 1751.7        | 336.9          |
| P7      | normal       | low                 | 0.1         | 4.6            | 529.5         | 424            | 23.2        | 2.8            | 1305.1        | 295            |
| P8      | normal       | –                   | 0.8         | 3.2            | 231.9         | 308.5          | 10.3        | 2.6            | 314.9         | 206.2          |
| P9      | normal       | intermediate        | 0.1         | 4.6            | 692.4         | 302.3          | 8.6         | 3.5            | 576.1         | 376.1          |
| P10     | normal       | low                 | 0.1         | 4              | 431.5         | 544.8          | 10.7        | 3.6            | 2642.6        | 765.1          |
| P11     | normal       | intermediate        | 0.8         | 3.7            | 392.1         | 394.4          | 1.9         | 3.1            | 486.8         | 436            |
| P12     | normal       | intermediate        | 0.4         | 3.6            | 1102.6        | 636.6          | 24.6        | 3.4            | 788.7         | 367.4          |
| P13     | normal       | high                | 0.1         | 3.9            | 913           | 178.1          | 3.5         | 2.8            | 57.4          | 58             |

CRP: C-reactive protein. LTSR: latency time of the swallowing reflex.
flow controller. The sensor signal is input into the PC at a sampling rate of 0.5 s and automatically analyzed by the analytic software to determine the concentration of the targeted gas components. Each targeted gas at ppb level can be simply measured by being sampled automatically from a sampling bag.

**Breath and saliva collection at bedside before breakfast.** Acetone and isoprene levels in breath were measured at bedside before breakfast on T1 (before oral care), T2 (the day after oral care but before operation), and T3 (after operation) during hospitalization. Patients were asked to exhale breath into 1 L Flek-Sampler® bags (Omi Odor-Air Service Co., Ltd., Tokyo, Japan). The bags were immediately connected to the nearby portable gas chromatograph, Gas Analyzer XG-100V. Breath in the bag was sampled for 10 s at 200 mL/min, and acetone and isoprene concentrations were directly read according to each retention time in 20 min. A new Flek-Sampler® bag was used for each measurement. Patients were asked to collect saliva into a sterilized tube by chewing a paraffin pellet (Orion Diagnostica Oy, Espoo, Finland) for 5 min. The saliva was brought to the lab immediately after collection. The number of bacteria in saliva was counted by an oral bacteria detection apparatus based on the dielectrophoretic impedance measurement method (DEPIM) (Panasonic, Inc., Tokyo, Japan) (14). Then, the saliva was divided into two aliquots (1 mL each) and incubated in screw-capped sterile test tubes under anaerobic and aerobic conditions. After incubation for 30–34 h, each tube was inserted into a 1 L Flek-Sampler® bag. The bag was filled with purified room air, and the tube was opened inside the bag. Acetone and isoprene contained in the air originating from the saliva were measured by the portable gas chromatograph XG-100V (New Cosmos Electric Co., Ltd., Osaka, Japan) through the bag.

**Perioperative sampling schedule.** Exhaled breath and saliva were sampled on T1 (before oral intensive care) and T2 (the day after oral intensive care) before operation. According to their postoperative conditions, 11 patients were sampled once on 2 to 8 days after operation. One patient (P6) was sampled on 3 days and 7 days after operation. Another patient (P4) was sampled on 7 days after operation and the day after diagnosis of postoperative pneumonia (21 days after operation). Routine blood examinations, including serum CRP and albumin, were performed before and after operation depending on need (Table 2).

**Statistical analysis.** All data are expressed as means ± SD, unless otherwise indicated. Distributions of continuous variables at 2 time points (T1 and T2, T2 and T3) were evaluated via Wilcoxon signed-rank tests. The relationships between breath (acetone or isoprene) and serum hepatic proteins (CRP or albumin) were evaluated by means of non-parametric Spearman’s rho test. Significance was indicated at \( P < 0.05 \). IBM SPSS Statistics for Macintosh, Version 22.0 (IBM Corp., Armonk, NY) was used for all calculations.

**RESULTS**

**Analysis of saliva**

The total number of bacteria in saliva was significantly different between T1 and T2 (Wilcoxon signed-rank test, \( P = 0.033 \)) (Fig. 1). We observed a decrease from T1 to T2, and no differences between T2 and T3. No isoprene or acetone was detected in gases originating from saliva after \textit{in vitro} incubation under anaerobic or aerobic conditions.

**Assessment of upper respiratory protective reflexes**

Twelve patients agreed to be examined for their upper respiratory reflexes before operation. None of them exhibited impairment of cough reflex. As for
swallowing reflexes, 4 patients were classified in the intermediate-risk group and 2 patients were classified in the high-risk group according to LTSR. One of two patients treated by introductory radio-chemotherapy was classified into the intermediate-risk group and another patient was in the high-risk group before operation (Table 2).

Relationship between breath and acute-phase proteins at perioperative phase
There was no correlation between breath acetone and CRP before operation; however, there was a significant correlation between acetone and CRP at postoperative phase (Spearman’s $\rho = 0.559$, $P = 0.03$) (Table 2, Fig. 2). There were no correlations between acetone and albumin before or after operation. As for isoprene, there were no correlations with albumin before operation, or with CRP before or after operation; however, there was a significant correlation between isoprene and albumin in postoperative phase (Spearman’s $\rho = 0.659$, $P = 0.008$) (Table 2, Fig. 3).

DISCUSSION
To minimize influences on metabolic state by diet and physical activity during hospitalization, we sampled exhaled breath and saliva at bedside between 7:00 and 7:20 before breakfast, and analyzed them within 30 minutes after sampling. The total number of bacteria in saliva decreased significantly after intensive oral care and no significant change was observed after operation (Fig. 1), indicating that intensive oral care before operation was useful to decrease salivary bacteria and thus prevent airway colonization in perioperative lung cancer patients. No acetone or isoprene was detected in gases originating from saliva after in vitro incubation under anaerobic or aerobic conditions. This suggests that salivary microbiota were not capable of producing acetone and isoprene in this study. Studies with selected ion flow tube mass spectrometry (SIFT-MS) have shown that breath acetone and isoprene are purely systemic, and our results are consistent with them (24, 28).

We compared perioperative exhaled breath and acute-phase proteins. Fig. 2 shows the positive correlation between exhaled acetone and CRP (Spearman’s $\rho = 0.559$, $P = 0.03$) at postoperative phase despite the lack of correlation before operation. As CRP is widely used as a sensitive marker of systemic inflammation and tissue damage (20), the level of CRP increases depending on surgical trauma in each patient after operation. An observational study about oxidative and metabolic stress during cardiac surgery shows exhaled acetone concentration increased slightly after sternotomy and remarkably after end of extracorporeal circulation when levels of catecholamines rose (19). They report that acetone concentrations were constant on a higher level after

Fig. 2  Relationship between CRP and acetone in preoperative (A) and postoperative (B) phases. There was a significant correlation between acetone and CRP in postoperative phase during hospitalization (Spearman’s $\rho = 0.559$, $P = 0.03$)
operation and exhaled acetone concentrations exhibited positive correlation to serum CRP. In our study it is possible that during surgery of lung cancer (lobectomy, wedge resection, pneumonectomy, chest wall resection and reconstruction) catecholamines were elevated to induce lipolysis which increased concentration of ketone bodies. Fasting during and after operation under influence of catecholamines may increase exhaled acetone concentration through lipolysis and ketogenesis (15).

Fig. 3 shows the positive correlation between isoprene and albumin (Spearman’s $\rho = 0.659$, $P = 0.008$) postoperatively, although there is no correlation before operation. Isoprene is an endogenous volatile organic compound that is a byproduct of cholesterol biosynthesis and is reported to reliably diagnose advanced liver fibrosis (1). A previous study shows reduction of breath isoprene after tumor resection in non-small-cell lung cancer patients and speculates isoprene could be the target of free radicals in oxidative stress process caused by operation (21). No patients had liver diseases such as liver fibrosis in our study. The range of isoprene concentrations among 13 patients tended to extend from pre-operation (98.8–636.6 ppb) to post-operation (0–765.1 ppb), possibly depending on each postoperative process. Serum albumin concentrations tended to decrease from pre-operation (range 3.2–4.6 g/dL, mean 3.9 g/dL) to post-operation (range 2.4–3.6 g/dL, mean 3.1 g/dL). Previous studies also report decreases in albumin concentrations in early postoperative phase after major surgery (18, 22). An increase in total body protein breakdown is one of the acute metabolic changes after operations. The physiologic meaning of albumin synthesis and its regulation after surgery, however, is not fully understood. Inflammatory cytokines and the release of corticosteroids also seem to affect the mechanism (11). The correlation between isoprene and albumin early after operation needs to be further explored to clarify the causal association.

Even with intensive oral care and evaluation of LTSR, one of the 13 patients (7.7%) developed postoperative pneumonia on the 20th day after operation. The diagnosis was based on the guidelines of the Japanese Respiratory Society (4, 23). The patient had been treated by introductory radio-chemotherapy before operation and his swallowing reflex was severely impaired (classified as high risk by LTSR). The values of serum CRP and exhaled acetone increased to 19.2 mg/dL and 1979.8 ppb, respectively, just after the diagnosis of postoperative pneumonia. At the same time, the values of serum albumin and exhaled isoprene decreased to 2.4 g/dL and near 0 ppb (not detectable), respectively. The combination of elevated CRP concentration and hypoalbuminemia is used as a systemic inflammation-based Glasgow Prognostic Score for patients with cancer (17). This score system highlights the need not only to treat the tumor but also the systemic inflammatory response. The combination of elevated acetone and decline of isoprene in exhaled breath might indicate the acute phase of the systemic inflammatory response in patients with postoperative pneumonia.

To the best of our knowledge, there are not many studies on perioperative changes in breath compounds in lung cancer. Changes in volatile organic
compounds during one-lung ventilation for lung operation was reported by Kischkel et al. (15). They sampled alveolar breath separately from healthy and diseased lungs before and after tumor resection. They found that acetone profiles were linked to metabolism and isoprene were exhaled independently from tumors and surgery. In our study, breath samples were taken at bedside after operation when patients restarted oral nutrition; however, the correlation between breath acetone and CRP in the early postoperative stages supports the previous results for acetone during one-lung ventilation. Regarding esophagectomy and gastrectomy, the response of breath acetone and isoprene to operation over one week was reported by Boshier et al. (3). They described that patients who developed pneumonia after esophagectomy tended to have lower breath isoprene levels at all postoperative time points. The positive correlation between exhaled isoprene and albumin at the postoperative phase in our study is consistent with their previous observations.

The advantages of our study are sampling at bedside before breakfast and evaluating breath with acute-phase proteins at perioperative period during hospitalization, considering change of oral microorganisms due to breakfast and impairment of upper airway reflex. However, the limitations are small number of subjects and that the values of acetone and isoprene were based on a single measurement in clinical situations.

Overall, the total numbers of oral microorganisms in saliva significantly decreased after intensive oral care among 13 patients before operation. Exhaled acetone and isoprene were confirmed to be derived from the body metabolism and were significantly correlated with CRP and albumin, respectively, at the early postoperative phase. Our results support the idea that breath acetone and isoprene have a possibility to reflect systemic inflammatory reactions and subsequent changes in metabolism early after operation of lung resection.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

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