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# Breath metabolite response to major upper gastrointestinal surgery

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ABSTRACT

*Background:* Esophagectomy and gastrectomy are associated with profound metabolic changes and significant postoperative morbidity. The aim of this prospective clinical study was to determine whether breath analysis can offer novel insight into the surgical metabolic response and identify biomarkers of postoperative complications, including lung injury.
*Methods:* Breath samples were collected preoperatively and at 24, 48, 72, 96 and 168 h after esophagectomy ($n = 25$) and gastrectomy ($n = 15$). Targeted analysis of four prominent breath metabolites was performed by selected ion flow-tube mass spectrometry. Patients with nonsurgical lung injury (community-acquired pneumonia) were recruited as positive controls.
*Results:* Perioperative starvation and subsequent reintroduction of nutritional input were associated with significant changes in breath acetone levels. Breath acetone levels fell after esophagectomy ($P = 0.008$) and were significantly lower than in gastrectomy patients at postoperative time points 48 ($P < 0.001$) and 72 h ($P < 0.001$). In contrast, concentrations of isoprene increased significantly after esophagectomy ($P = 0.014$). Pneumonia was the most frequently observed postoperative complication (esophagectomy 36% and gastrectomy 7%). The concentration of hydrogen cyanide was significantly lower in the breath of patients who developed pneumonia, 72 h after surgery ($P = 0.008$). Exhaled hydrogen cyanide ($P = 0.001$) and isoprene ($P = 0.014$) were also reduced in patients with community-acquired pneumonia compared with healthy controls.
*Conclusions:* Selected ion flow-tube mass spectrometry can be used as a totally noninvasive resource to monitor multiple aspects of metabolic alterations in the postoperative period. Exhaled concentrations of several prominent metabolites are significantly altered after major upper gastrointestinal surgery and in response to pneumonia.


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## 1. Introduction

Highly invasive surgical procedures, such as esophagectomy and gastrectomy, are associated with an intense inflammatory and metabolic response, characterized by the release of cytokines, inflammatory mediators, and prolonged perioperative starvation [1–8]. Accordingly, patients undergoing these surgeries experience high rates of postoperative complications, primarily involving the lungs [9,10]. While many studies have sought to determine the metabolic and inflammatory changes to these surgeries within the fluid phase, the analysis of metabolites within exhaled breath could potentially offer a complementary and as yet unexplored, strategy.

Analysis of trace gases within exhaled breath, for the purpose of noninvasive disease detection, is a rapidly emerging field of medical research, which builds on previous breakthroughs in mechanistic, diagnostic, and monitoring aspects of pulmonary and systemic metabolism [11]. Since the initial report of Pauling *et al.* [12] in the early 1970s, hundreds of trace gases have been identified in human breath [13]. Although some of these compounds are anticipated to be of exogenous origin, and hence are of limited diagnostic potential, others are derived endogenously.

While there are numerous proposed applications for breath testing in medicine, recently there has been increasing efforts to apply breath analysis to monitoring of metabolic and inflammatory processes related to surgery and critical illness [14–23]. Specific events that are predicted to induce characteristic changes in breath metabolite levels in response to major surgery include oxidative stress; the systemic inflammatory response syndrome; infection, and; perioperative starvation [16]. The impact of these events on breath metabolites have not been explored in the setting of major gastrointestinal surgery.

The primary objective of this study was to use selected ion flow-tube mass spectrometry as a powerful and sensitive instrument to detect a judiciously selected panel of metabolites simultaneously from the breath of patients undergoing major upper gastrointestinal surgery. The main focus was to monitor the patient journey in the postoperative period. Metabolites targeted were those predicted to be implicated in surgical metabolic and oxidative stress. The second objective of the study was to compare two major surgical approaches. Esophagectomy and gastrectomy are both invasive surgeries but esophagectomy also includes opening the thoracic cavity and the requirement for periods of one lung ventilation, which appears to impact on the systematic inflammatory response and the development of respiratory complications. The final aim was to explore whether selected breath metabolites could reflect changes in postoperative nutritional status and the development of pulmonary complications.

## 2. Methods

### 2.1. Patients

Local ethics committee approval was obtained for the present study, and all patients provided informed written consent before enrollment.

All patients undergoing elective esophagogastric resections at St Mary's Hospital (Imperial College Healthcare NHS Trust) during an 11-mo period were invited to take part in the present study. To further distinguish between the degrees of surgical stress, patients were divided into those undergoing either esophagectomy or gastrectomy. Esophagectomy was via either a two-stage (Ivor Lewis), three-stage, or thoracoabdominal approach. Gastric resections involved either partial or complete gastrectomy.

Patient demographics and perioperative variables were collected and recorded in a prospectively maintained database. In addition, the following parameters were also collected at the time of breath sampling: physiological variables (heart rate, blood pressure, respiratory rate, oxygen saturation, and temperature), serum parameters (albumin, creatinine, hemoglobin, neutrophil count, and C-reactive protein), and where an arterial line was *in situ* the results of arterial blood gas analysis (pH, bases excess, $PaO_2$, $PaCO_2$, lactate, and glucose). The diagnosis of postoperative complications was in accordance to predefined criteria (full details of criteria used to diagnose postoperative complications are provided online as supplementary material). Specifically, the diagnosis of postoperative pneumonia was based on radiographic, microbiological and clinical evidence of pneumonia. Acute respiratory distress syndrome (ARDS) and acute lung injury were diagnosed using the American–European Consensus Conference definitions [24].

To more clearly delineate the gas phase metabolic effects of surgery and respiratory tract infection, breath samples were also collected from patients admitted to St Mary's Hospital with a confirmed diagnosis of community-acquired pneumonia (CAP) (full details of criteria used to diagnose CAP are provided online as supplementary material). Healthy controls were recruited from the partners of patients attending accident emergency or outpatient departments.

### 2.2. Breath sample collection

Breath samples were collected preoperatively (typically the night before surgery) and at 24, 48, 72, 96, and 168 h after surgery. Breath samples from patients with CAP were collected at a single time point within 24 h of admission.

Off-line mixed-breath samples (~2 L) were collected by asking patients and control subjects to exhale, after inhalation to near total lung capacity, directly into double thickness Nalophan sample bags (Kalle UK Ltd, Witham, United Kingdom). All subjects were required to have fasted for a minimum of 1 h before breath sampling so as to diminish the potential for oral contamination of samples.

### 2.3. Breath analysis by selected ion flow-tube mass spectrometry

All samples were analyzed by selected ion flow-tube mass spectrometry (SIFT-MS). A detailed description of the SIFT-MS technique and its applications are provided elsewhere [25]. Briefly, SIFT-MS relies on the generation of specific precursor ions ($H_3O^+$, $NO^+$, and $O_2^+$), which are individually selected and injected into a flow tube, carried by a fast-flowing helium