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Standardized Protocols for Measuring Volatile Sulfur Compounds: Scientific Foundations and Methodologies

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Halitosis is defined as a nasty odor emanating through the mouth and is primarily related to the enhanced concentration of volatile sulfur compounds (VSCs). VSC measurements have been commonly used for experimental comparison and clinical diagnosis. As quantitative methods for comparative analyses of oral malodor, gas chromatography devices have been most commonly used to quickly and easily determine the concentration of several gas components of VSCs, which are agents primarily responsible for halitosis. The concentrations of VSCs fluctuate dynamically depending on contributing factors, including various oral/systemic conditions, intake of medicine and food/drink, oral hygiene, and even routine daily activities. Therefore, the exact analysis of VSCs requires the appropriate standardization of not only exact measurement techniques but also participant conditioning with scientific considerations. Thus, this paper describes the experimental standardizations commonly recommended in previous literature and their scientific background.

Keywords: Analysis; Gas chromatography; Halitosis; Method; Standardization; Volatile sulfur compounds

INTRODUCTION

Halitosis, an unpleasant or foul smell coming from the mouth, is a common problem worldwide. It has negative social implications for sufferers and interpersonal relations. Most cases of halitosis could mainly originate from intraoral sources, where the condition is often referred to as oral malodor [1]. Oral malodor is basically provoked by the influx of foul-smelling intraoral agents into the exhaled breath. These agents include volatile sulfur compounds (VSCs) and other odorous compounds such as putrescine, indole, skatole, and cadaverine [2].

Halitosis can be evaluated using two main methods: subjective organoleptic judgments of oral malodor and objective instrumental assessments of VSCs. Although the organoleptic method of smelling with the examiner's nose is considered the gold standard for assessing halitosis, it is not always reliable because it is based on the subjective judgment of the examiner. Additionally, the subjective method is considered not suitable to determine the absolute value of oral malodor intensity. Moreover, providing the measurable difference in odor intensity among subject groups, between pre-/post-treatments, or among treatments is very difficult [3]. Therefore, for the clarification and comparison of odor intensity, the objective detection and measurement of oral odorous substances using an instrument are

usually employed for clinical and experimental purposes [3]. Despite the application of measuring instruments, the amounts of each odorous substance emanating from the mouth and body highly vary daily and, sometimes, dramatically changes depending on daily events including sleep, food intake, tooth/tongue brushing, application of oral cleansing agents and body deodorants, local/systemic diseases, and daily medications. Accordingly, any experimental research on oral malodor requires careful establishment of experimental conditions and techniques for more accurate and reliable data acquisition by minimizing the influence of possible contributing factors.

Therefore, this study aimed to present experimental conditions and their scientific backgrounds through an extensive review of the previous literature.

MAIN TEXT

Human breath is a highly complex mixture of numerous odorants that can cause unpleasant conditions such as halitosis [4]. The etiology of halitosis is now considered multifactorial, probably involving complex interactions among local, systemic, physiological, and pathological factors (Table 1). Halitosis has various causes, which are broadly classified into intraoral and extraoral causes, including poor oral hygiene, dry mouth, periodontal diseases, tobacco/cigarette smoking, alcohol consumption, dietary habits, obesity, diabetes, stress, aging, personal hygiene, and intake of certain medications [5]. Therefore, the contributing factors must be properly controlled for a more reliable measurement of VSCs. An appropriate experimental design for better reliability should be established throughout the experimental step, including the selection of participants, preconditioning of participants, and handling of the measurement device.

1. Participant Selection

1) Inclusion criteria

For the comparative study between experimental and control groups, matching participants by age and sex may control for potential variability in the results. This approach acknowledges that while some studies have not found significant effects of age or sex on oral malodor, others have suggested a possible relationship between these factors and variables such as tongue coating and malodor intensity [5-13]. A previous study reported that VSC concentrations in morning breath were significantly higher in women than in men [12]. Furthermore, there could be changes in VSC

Table 1. Extraoral and intraoral causes of bad breath [19]

Effects of extraoral disorders and medications	
Respiratory disorders	Sinusitis, tonsillitis, tonsilloliths, etc.
Gastrointestinal disorders	Esophageal reflux, gastrointestinal inflammations, pyloric stenosis or intestinal obstruction, malabsorption syndromes, enteric malignancies, etc.
Metabolic disorders	Adult type 2 diabetes mellitus, pediatric type 1 diabetes mellitus, renal failure, alcoholic ketoacidosis, Lignac disease, homocystinuria, liver cirrhosis, maple syrup urine disease, methionine adenosyl transferase deficiency, phenylketonuria, trimethylaminuria, chromosome 15 deficiency, etc.
Medications and health supplements	Aminothiols (cysteamine), acid reducers (ranitidine), anticholinergics (oxybutynin and glycopyrrolate), antidepressants (imipramine and duloxetine), antihistamines (astemizole), antispasmodics (colpermin), chemotherapeutic agents (PX-12 and sylibin phytosome), health supplements (fish oil, peppermint oil, rosehip supplement powder, selenium, and vitamin E), sulfoxide, diclofenac, steroids (astemizole and beclomethasone dipropionate), etc.
Effects of intraoral disorders	
Odontogenic and peri-odontogenic disorders	Fixed orthodontic appliances, odontogenic causes (insufficient or inadequate oral hygiene, plaque, tooth decay, food impaction, and poorly sanitized acrylic dentures), herpetic gingivitis, peri-implantitis, pericoronitis, periodontal diseases (gingivitis and periodontitis), etc.
Non-odontogenic disorders	Malignant or benign primary tumors, oral candidiasis, recurrent oral ulcerations, tongue coating, other stomatitis, etc.

levels during the menstrual cycle [9,13]. In a previous study, a female participant with periodontitis showed a 2.2-fold increase in VSC levels during the ovulation phase compared with the follicular phase [9]. Another study showed a distinct tendency for the compound to increase two- to four-fold around the middle of the cycle and menstruation [13]. Although some studies have reported diverse changes in VSC concentrations according to the menstrual stages, their findings implied that the menstrual cycle could also be considered to minimize the possible effects of female sex hormones during the halitosis experiment.

2) Exclusion criteria

(1) Habits: Numerous studies have reported that current smokers are more likely to suffer from halitosis, which is possibly caused by the disturbance of the oral microbiota and the oral environment [14-16]. Therefore, several studies have recommended that participants refrain from using tobacco products for 4-12 hours before assessments [17,18].

(2) Pathological conditions and medications: Approximately 10%-20% of halitosis cases could be due to nonoral causes [19]. Representative causes of extraoral halitosis include respiratory, gastrointestinal, endocrine, and hematologic system diseases [19]. Among nasal origins, chronic sinusitis may be the major cause of halitosis originating from the nose. A study considered that the purulent material from chronic sinusitis falls on the tongue coated with microbiota, which promotes VSC production [20]. Recurrent tonsil and adenoid infections cause chronic follicular tonsillitis, frequently inducing the accumulation of saliva, food, and necrotic substances. Tonsilloliths easily occur when these accumulations are not removed, increasing the risk of oral odor approximately 10-fold [21]. Approximately 0.5% of halitosis cases result from gastrointestinal disorders such as esophageal and gastric outlet strictures that make it difficult for foods to pass into the stomach, thereby keeping them in the esophagus and causing oral malodor [22]. Several metabolic diseases, including diabetes mellitus, renal disease, liver cirrhosis, and other diseases, may manifest with unique malodors depending on their metabolic pathophysiologies [22]. Patients with chronic renal failure may have urine-smelling breath caused by relatively high urea nitrogen levels in the blood and reduced salivary flow [23]. Patients with abnormal liver function may have a sweet and fecal odor in their breath.

Previous studies have described that numerous medicines and health supplements could change the profiles of compounds in the oral and/or exhaled breath by altering volatile metabolites and disturbing the microbial environment [17,24,25]. Extraoral halitosis-causing medications include aminothiols (cysteamine), antifungal agents (voriconazole), acid reducers (ranitidine), antidepressants (imipramine and duloxetine), anticholinergics (oxybutynin and glycopyrrolate), antihistamines (astemizole), antispasmodics (colpermin), steroids (beclomethasone dipropionate), chemotherapeutic agents (PX-12 and sylibin phytosome), health supplements (fish oil, peppermint oil, selenium, rosehip supplement powder, and vitamin E), dimethyl sulfoxide, and diclofenac [19,24].

Regarding health supplements, peppermint oil (187 mg/capsule) is used to relax the muscles of the gastrointestinal system and causes halitosis in 13.1% of patients with irritable bowel syndrome [26]. Some studies have revealed that fish oil supplementation of 1.84-12 g/day dose-dependently increased the prevalence of halitosis [7,27]. Furthermore, the dosage of fish oil was directly correlated with the incidence of halitosis. A study reported that oral administration of 2,250-4,500 mg/day rosehip supplement powder along with 80 mg/day of vitamin C resulted in halitosis in 14% of the intakes [28]. Several studies have reported that selenium supplements, such as selenomethionine and sodium selenite, cause halitosis in 60%-90% of patients [29,30]. Therefore, a literature recommendation for organoleptic assessment of halitosis is to complete antibiotic therapy for at least 4-8 weeks before assessments [17].

Regarding the effect of dry mouth, a study reported that the flow rate of resting saliva is significantly lower in patients with strong oral malodor than in those with no or mild oral malodor, suggesting that saliva flow rate is a significant regulatory factor for oral malodor [31]. Another study revealed that dry mouth was highly significantly and directly correlated with the occurrence of halitosis [15]. Regarding the effect of oral pathologic conditions, freshly collected saliva contains very low concentrations of free amino acids. However, the saliva of patients with active periodontitis contains numerous disrupted epithelial cells.

Moreover, the cells were covered with considerably more bacteria than those from healthy participants without periodontal disease. Concomitantly, the increased number of damaged leukocytes could enter the oral cavity through the disintegrated epithelial lining. Gingival hemorrhage is frequently associated with gingivitis and periodontitis. Hematic and cellular elements provide crucial substrates for odor production, subsequently facilitating bacterial growth and accelerating the proteolysis and odor production of putrescent saliva [32]. Therefore, individuals with active periodontal diseases were excluded to omit the potential effect of pathologic putrefactive conditions. In addition, a previous study provided the inclusion criteria of the presence of at least 24 teeth and the absence of fixed or removable prostheses or orthodontic appliances [33]. Dentures can be another source of oral malodor, particularly if participants wear them overnight or do not clean them [34]. Oral malodor in wearers of complete dentures is significantly related to oral dryness and tongue coating. Numerous studies have also reported that this condition is caused by dental caries, ulcerative lesions or wounds, food impaction, wearing dentures at night, and fixed functional appliances (Table 2) [35,36].

2. Pre-Experimental and Experimental Conditioning

1) Diet and water intake

A previous study revealed the relationship between daily alcohol consumption and strong malodor [37]. This study reported that the daily alcohol consumed group had significantly higher VSC concentrations than the "sometimes" and "no alcohol" groups. The mechanism by which alcohol aggravates oral malodor might be more related to the decreased saliva flow rate and aggravated periodontal disease than to the increased production of volatile acetaldehyde excreted by the lungs [37].

Certain foods, including garlic, onions, and some spices, contain high levels of various sulfur compounds. Some of these sulfur compounds were degraded by intraoral bacteria immediately after intake, and the majority of them were metabolized mainly in the liver and excreted via the lungs and other routes after enteral absorption [38]. For garlic, the concentration of allyl mercaptan, one of the initial garlic flavorants, peaked 1 or 2 minutes after ingestion and then declined to baseline values within approximately 1 hour. Contrary to the initial flavorants, the concentration of allyl methyl sulfide, a delayed garlic flavorant, peaked 4 hours after ingestion and was prolonged for 30 hours, indicating that it was a product of systemic metabolism [39]. Therefore, a previous study recommended that for organoleptic assessment of halitosis, a participant should avoid eating spicy foods, particularly those containing onions and garlic, for 24–48 hours before assessments [17].

Rinsing with water could be effective for 15 minutes [40]. A previous study showed by organoleptic assessment that water slightly reduces breath odor in 30 minutes [41]. Despite this finding, a previous study recommended that participants refrain from drinking water within 1 hour before their appointment [17].

Regarding meals, eating could decrease VSC concentrations over several hours after meals by modulating the oral environment and subsequent microbiomes [42,43]. A

Table 2. Experimental protocols usually applied for participant selection [17,18]

Inclusion criteria	
Age	Age distribution matched among different groups
Sex	Sex ratio matched among different groups
Systemic condition	Generally healthy without any identified diseases/disorders
Exclusion criteria	
Medicines/health supplements	Not completed for at least 4–8 wks before the assessments
Systemic diseases affecting VSC concentration	Presence of uncontrolled affection diseases/disorders (e.g., diabetes mellitus, hepatic diseases, and renal diseases)
Oral diseases affecting VSC concentration	Presence of uncontrolled affection diseases/disorders (e.g., gingivitis, periodontitis, pericoronitis, dry mouth, and mucosal ulcer/inflammation)
Number of remaining teeth	<24
Dental prosthetics	Usage of removable prosthetics

VSC, volatile sulfur compound.

previous study showed that the concentrations of CH_3SH and H_2S were depressed for at least 2 hours after eating a meal [43]. Another study revealed that daily events, including awakeness, meals, and oral hygiene activity, could cause diurnal cyclical changes in malodor intensity [42]. Oral malodor generally tends to be strongest immediately after waking up in the morning because of the lack of physiological stimuli such as chewing and swallowing during sleep. The absence of physiological stimuli can cause a dramatic decrease in salivary secretion and self-cleansing functions, thereby enhancing the microbial environment and production of VSCs [44]. Accordingly, the concentration of VSCs in the mouth markedly increased after every awakening [42]. In contrast, eating decreased the concentration of VSCs by not only saliva stimulation but also by removing the exfoliated epithelial cells and bacteria by swallowing [42,45]. Breath odor scores decreased within 2 hours after intake of food and coffee [17]. Therefore, a previous study recommended that participants refrain from eating and drinking beverages within 12 hours for the morning assessment or within 4 hours for the afternoon assessment [17].

2) Oral hygiene

A previous study revealed that oral hygiene activities, including tooth brushing and tongue cleaning, could affect the levels of VSCs in mouth air for ≥4 hours [42]. Therefore, several studies have recommended that participants refrain from performing oral hygiene procedures, such as using mouthwashes or breath fresheners within 12 hours for the morning assessment or within 4-6 hours for the afternoon assessment [17,46].

3) Timing and experimental room conditions

Morning breath upon awakening usually has a short duration and is then reduced quickly after breakfast [12]. For the morning measurement, it would be more reasonable to perform the measurement within the determined time range under clear instructions on breakfast. Although some studies have allowed their participants a light breakfast, others did not, most prefer early morning without permitting any breakfast for better clearance of experimental conditions [12,17,33,47].

4) Usage of aromatic products

Manufacturers of Oralchroma® (FIS Inc.) and other devices recommend avoiding any gasses and chemicals around the device [48]. Therefore, participants should refrain from wearing cologne, perfume, scented hairsprays, or strongly scented cosmetics at their assessment appointments [17]. Thus, participants must avoid using scented cosmetics 24 hours before the assessment (Table 3) [18].

3. Experimental Devices

To measure VSCs, electrochemical sensors (e.g., Halimeter® [InterscanCo.]) and portable gas chromatographs (e.g., OralChroma®, TwinBreather® [iSenLab Inc.]) are commonly used [49]. A previous study indicated that OralChroma® may provide a more comprehensive assessment of VSC production by oral microflora than Halimeter® [46]. Another study showed that OralChroma® could be a highly sensitive device for measuring VSCs, such as standard gas chromatography. In addition, it could perfectly differentiate between intra- and extraoral blood-borne halitosis, whereas the halometer could only detect intraoral

Table 3. Experimental protocols usually applied for participant instruction [17,18]

Water intake	Refrain from drinking water within 1 h before the appointment
Food/drink intake	Refrain from eating, drinking beverages within 12 h for the morning assessment or within 4 h for the afternoon assessment
Spices intake	Refrain from eating spicy foods, particularly those containing garlic and onions, for 24-48 h before assessments
Use of tobacco	Refrain from using tobacco products for 4-12 h before assessments
Oral hygiene	Refrain from performing oral hygiene procedures, using oral rinses, or using breath fresheners within 12 h for the morning assessment or within 4-6 h for the afternoon assessment
Measurement timing	Usually early morning without permitting any breakfast
Use of scented cosmetics	Avoid using scented cosmetics for 24 h before the assessment
Measurement procedures	Procedures following the manufacturer's guideline
Equipment maintenance	Regular equipment maintenance based on the manufacturer's guideline

halitosis [50]. Accordingly, OralChroma® is currently one of the most practical devices for measuring the VSC concentration. The manufacturer of OralChroma® recommended revision of the device every 2 years for accurate measurement even if the device has not been [48]. Any measurement in patients who consumed alcohol must be avoided because it might damage the device. If this occurs accidentally, allow the OralChroma® to run for 24-48 hours so that the sensor can remove all alcohol remaining in the operating circuit, and the device can be recalibrated [48]. It was recommended to replace the gas inlet rubber plug after 200 usages and the sensor and column after 10,000 usages [48]. In addition, the detailed procedure for the measurement was provided in the user's guidebook by the manufacturer. Each procedure was required to follow the user's guidelines.

CONCLUSION

The experimental protocol for measuring VSC concentrations must be well-standardized for better reliability and accuracy. In particular, when subtle alterations in VSC levels are identified, the influences of the contributing factors must be minimized because VSC levels tend to change dynamically according to oral/systemic conditions, intake of medicine and food/drink, oral hygiene, and even routine daily activities. Therefore, a better understanding of the scientific background underlying the recommended protocols is essential for the exact measurement of VSC concentrations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets used in this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: JYK, JKJ. Formal analysis: JYK, JRK. Funding acquisition: JKJ. Methodology: JSB, JKJ. Project administration: JKJ. Writing - original draft: JYK, JKJ. Writing - review & editing: JKR, JSB, JKJ.

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