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The future of early disease detection: applications of e-nose technology in otolaryngology.

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Abstract

Introduction: Recent advances in electronic nose (e-nose) technology and successful clinical application are providing new methods for the rapid near-patient diagnosis of disease. There is real clinical need for new diagnostic tools in otolaryngology.

Materials & Methods: A critical review of recent advances in e-nose technology and current applications in otolaryngology is presented.

Results: The literature demonstrates evidence of accurate diagnosis in common otolaryngological conditions such as sinusitis (acute and chronic), chronic suppurative otitis media, otitis externa and nasal vestibulitis. A significant recent development is the successful identification of biofilm versus non-biofilm producing *Pseudomonas* and *Staphylococcus* species.

Conclusions: E-nose technology holds significant potential for rapid, non-invasive, point of care diagnosis of disease in otolaryngology.

Keywords

Electronic nose (e-nose), diagnosis, biofilms,

Introduction

Since the time of the ancient Greeks, physicians have been aware that it is possible to smell disease on the breath of those afflicted. An obvious example of this is the pear drop like smell of acetone in the breath of a diabetic. The human nose can be highly trained as an analytical tool for the discrimination or detection of odours from food (e.g. fish, meat, cheese and wine) and perfumes (cosmetics, soaps). However, there may be health and safety related issues and questions regarding inter-observer variability and sensitivity over time.[1] To overcome these difficulties sensor arrays have been used to develop electronic nose (e-nose) technology to mimic olfactory discrimination based on volatile production patterns.

Since the 1960's attempts have been made to build an artificial olfactory model to mimic the olfactory sense of mammals that can detect and discriminate the production of volatile compounds. Early instruments detected odours using mechanical noses based on redox reactions moving towards electronic nose technology in the 1980's. The currently accepted definition of an electronic nose was proposed by Gardner and Bartlett, in 1994: "An electronic nose is an instrument which comprises an array of electronic chemical sensors with partial sensitivity and an appropriate pattern recognition system, capable of recognising simple or complex odours".[2] The odorant molecules which are interact with the sensor array surfaces in the electronic nose (and to the olfactory system) are typically hydrophobic and volatile due to their molecular weight (30-300 Da), strength of the interactions between molecules and molecular shape.
Volatile organic compounds (VOCs) are organic compounds that can easily become gases or vapours; as such they can be detected in breath and bodily fluids. Many studies have shown that for certain pathological conditions such as infection, malignancy, liver and cardiopulmonary disease, specific patterns of VOCs, so called "volatile fingerprints", can be detected. This approach has been used to detect the presence of TB in sputum samples (Turner and Magan, 2004) and more recently been sued to discriminate between dermatophytes (Sahgal et al., 2007). Thus, potential exists to utilise this approach for more accurate diagnosis of disease.

An example of an E-nose device is shown in Figure 1. It mimics the olfactory sense of mammals. In humans smells are sensed by olfactory sensory neurons in the olfactory epithelium. Volatile molecules bind to olfactory neuron cell receptors producing a change in conformation which induces signal transduction to the brain. The active materials of the sensor array in an electronic nose device (=olfactory receptors) interacts with the VOCs resulting in a change in the binding surface of each sensor (change in resistance or conductance) which is transmitted to the pre-processor (olfactory bulb) where the output is amplified and the noise is reduced. In the final stage the simplified signals (=nerve impulses) as patterns of responses are processed by the data analysis system (=hypothalamus and olfactory cortex in the brain). This type of technology can be used as a novel rapid technology which can be exploited for the diagnosis of diseases and perhaps improve choice of most appropriate drugs to administer. [3]

Otolaryngology has probably the highest number of patients with the commonest range of symptoms in the field of medicine (otitis externa, rhinorrhea, discharging ears etc). The electronic nose approach offers many potential benefits to the speciality, because it is non-invasive, rapid and a relatively portable diagnostic tool. This review will demonstrate that preliminary applications have already demonstrated successful results and we believe it can become a substantial tool for the modern ENT department. One area of particular interest is

the diagnosis of biofilms. Recently two very extensive and interesting reviews have been published highlighting the importance and correlation of biofilms in Otolaryngology. [4,5]

Search Strategy

In order to define the current evidence for the role of e-nose technology in otolaryngology, a literature review was undertaken. The following electronic databases were searched, Medline (1952-2009), Embase (1974 -2009), Cinahl(1937 -2009), and the Cochrane Library (1996 - 2009) to source the relevant key texts, references, and reviews. Initially a review of all applications of e-nose technology was under taken, this was then focused onto clinical applications. Finally combinations of the following keywords were used: "e-nose", "electronic nose", "infection", "otolaryngology", "ENT", "biofilms" to hone in on applications relevant to otolaryngology. Four studies, detailed in Table 1, matched our criteria referring to the use of e-nose in ENT infections and one of them demonstrated the benefit of the technology e in detecting biofilms. The studies identified are detailed below and the evidence presented is discussed.

Applications of e-nose technology

Non medical applications

E-nose technology has been widely employed outside of the medical field. Much work has been done in the food industry on detecting the early microbial spoilage and non-microbial tainting of food with applications as wide ranging as monitoring the freshness of stored fish[6] and meat, to the classification of a wide range of beverages such as coffee, beer, wine.[7] There is significant interest in detecting the levels of mycotoxins produced by fungi in many food products. Thus, diverse studies have been carried out to differentiate between mycotoxigenic and non-mycotoxigenic strains of *Fusarium*, *Aspergillus*, *Penicillium* in food raw materials.[8,9] Enose technology has also been employed to detect mould growth on books stored in libraries.[10]

Clinical applications of e-nose technology

Many pilot studies utilising e-nose technology for the diagnosis of tuberculosis, [11] *Helicobacter pylori*,[12] renal failure,[13] urinary tract infection,[14] skin fungal infections,[15] ventilator acquired pneumonia,[16,17] cancer (lung,[18,19] breast[20]), acute asthma[21], have been completed. Each demonstrated promising results of e-nose technology as an adjuvant method of disease detection, offering the potential for rapid and non-invasive diagnosis currently unavailable to the clinician.

Table 2 provides further information on the studies highlighted above, detailing samples analysed and the VOCs used to detect the disease in each of the clinical studies. A number of reviews of the clinical applications of e-nose technology have been published. [22,23,24]

Although wide ranging clinical applications of e-nose technology have been examined in the literature, only four studies matched our criteria referring to the use of e-nose in ENT infections and one of these demonstrated the benefit of e-nose technology in detecting biofilms.

Otolaryngology and e-nose

Current applications of e-nose technology in otolaryngology

Most recent clinical applications of e-nose technology have been focused on are in the field of the otolaryngology. Various studies have shown evidence of e-nose effectiveness (high accuracy) in common otolaryngological conditions such as infection[25] and acute and chronic sinusitis.[26,27] Shyknon et. al.[25] using a commercial portable electronic nose (Cyranose C320) recruited 90 patients with various ENT pathologies including otitis externa, chronic suppurative otitis media and nasal vestibulitis.

Swabs were taken and analysed using the e-nose device before microbiological culture. Results showed the the e-nose had a sensitivity of 88.2% when compared with the gold standard of microbiological culture.

Thaler et.al.[26] in 2006 showed the potential of this approach by diagnosing bacterial sinusitis. She used a nasal continuous positive airway mask to sample gas exhaled through the nose of patients with sinusitis and compared this with controls.

In this study patients were considered infected if there was a positive culture from the swab sent to microbiology.She was able to predict correctly the diagnosis of sinusitis in at least 72% of samples and to identify infected versus non-infected patients 82% of the time.

Bruno et. al.[27] demonstrated the diagnostic usage of the electronic nose studying patients suffering from chronic rhinosinusitis (CRS). They performed a controlled study dividing the patients into two groups, the ones suffering with CRS and the healthy ones. The results showed figures as a high as 85% for the detection of the bacteria in patients with chronic rhinosinusitis compared to healthy individuals using e-nose technology.

One of the most exciting recent developments was the work done by Thaler et. al. [28] showing that the e-nose could successfully identify biofilm versus non-biofilm producing bacterial strains. Their results showed that the e-nose was able to correctly classify biofilm and non-biofilm producing mutant strains of *Pseudomonas* and *Staphylococcus* species with an accuracy range of 72.2 to 100%"

This has opened a new chapter in the clinical application of e-nose technology, due to recent data that links biofilms to common antibiotic resistant ear nose and throat infections. Biofilms are found in cholesteatoma,[29], tympanostomy tubes,[30] chronic tonsillitis,[31] OME,[32] speech valves,[33,34]. cochlear implantation[35,36] and sinusitis.[37,38,39,40] A biofilm is a complex aggregation of microorganisms that have been shown to play a major role in many chronic antibiotic resistant otolaryngologic infections.[41] Biofilms are very difficult to eradicate because they are enclosed within a matrix that can restrict the diffusion of substances and bind antimicrobials. This enables effective resistance by biofilm cells against large molecule, especially anti-microbial proteins such as lysozyme and complement.[42] Therefore a non-invasive method of diagnosing them rapidly in the clinic would be of great benefit and further investigation is warranted.

Discussion and Conclusions

E-nose technology has great potential for the diagnosis of diseases due to its rapid detection, simplicity, non-invasive application and demonstration of high levels of sensitivity in pilot studies undertaken to date. Potential applications of e-nose technology include implementation as a diagnostic tool for the identification of patients with particularly virulent and medically recalcitrant forms of chronic otolaryngologic infections. The recent report identifying biofilm versus non-biofilm species using e-nose technology is particularly exciting. The field of Otolaryngology has many potential applications of the technology with many patients having very common and every day conditions which are difficult to differentiate in the outpatient setting, but which the e-nose could be used to identify and enable earlier targeted treatments to be delivered.

The promise of rapid near patient testing enabling identification of causative species thus facilitating immediate prescription of targeted antibiotics has many advantages. Multi-centre clinical studies are required to validate the pilot studies undertaken to date and further evaluate the potential of this exciting technology.

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TABLE I
Clinical applications of enose technology.

Disease / Pathology	**Sample**	**Volatile Compounds**	**Results**	**Reference**
Tuberculosis	Sputum	hexacosanoic acid	100% correct classification of Mycobacterium tuberculosis other related bacteria	9
Helicobacter pylori	Gastric juice			12
Renal failure		phenylacetic acid,		13
Urinary Tract Infection	Urine	Isovaleric acid, alkanes	Identification of species of causative bacteria the sensitivity and specificity were 83.5 and 87.6%, respectively.	14
Skin fungal infections				15
Ventilator acquired pneumonia	Breath	Nitric oxide	Accuracy of at least 80% comparing e-nose to chest CT	16,17
Breast cancer	Human Breath	Alkanes Monomethylated alkanes	The breath test distinguished between women with breast cancer and healthy volunteers with a sensitivity of 94.1% (48/51) and a specificity of 73.8% (31/42) (cross-validated sensitivity 88.2% (45/51), specificity 73.8% (31/42))	20
Lung cancer	Human Breath	Alkanes Monomethylated alkanes	For stage 1 lung cancer, the 22 VOCs had 100% sensitivity and 81.3% specificity.Cross-validation of the combination correctly predicted the diagnosis in 71.7% patients with lung cancer and 66.7% of those without lung cancer	18,19
Acute asthma	Human Breath	Pentane	Peak expiratory flow rates were 202+/-29 L/min during acute asthma and 327+/-26 L/min once acute asthma subsided ($p<0.05$). Exhaled pentane levels were 8.4+/-2.9 nmol/L during acute asthma and decreased significantly to 3.5+/-0.5 nmol/L once acute asthma subsided	21



Figure 1: An NST 320 e-nose (Applied Sensors, Sweden) used for clinical studies..

Table II

Summary of the four studies investigating the application of E-nose technology to Otolaryngology

Study	Publication Year/Journal	Patients/specimens included	Outcome
Shykhon ME et al	2004/ Journal of Laryngology and Otology	90 bacterial swabs from 90 patients with ENT infections	Electronic nose was correct in 88,2 of cases comparing with microbiolgy
Thaler ER et al	2006/ American journal of rhinology	11 patients Nasal exhalations sampled	72% correct precidiction of sinusitis
Bruno et al	2008 European archive Otorhinolaryngology	28 patients ,14 with CRS and 14 healthy Nasal swabs taken from middle meatus	Accuracy as high as 85% in patients with CRS
Thaler et al	2008 American journal of rhinology	Biofilm and non biofilm producing mutant strains of Pseudomonas and Staphylococcus were incubated and sampled by e-nose	Electronic nose was able to indentify biofilm versus non biofilm with accurancy ranging from 72 to 100%



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