The Laryngoscope
Lippincott Williams & Wilkins, Inc.

Diagnosis of Pneumonia With an Electronic Nose: Correlation of Vapor Signature With Chest Computed Tomography Scan Findings

Neil G. Hockstein, MD; Erica R. Thaler, MD; Drew Torigian, MD; Wallace T. Miller, Jr., MD; Olivia Deffenderfer; C. William Hanson, MD

Objectives/Hypothesis: **The electronic nose is a sensor of volatile molecules that is useful in the analysis of expired gases. The device is well suited to testing the breath of patients receiving mechanical ventilation and is a potential diagnostic adjunct that can aid in the detection of patients with ventilator-associated pneumonia.** ***Study Design:*** **A prospective study.** ***Methods:*** **We performed a prospective study of patients receiving mechanical ventilation in a surgical intensive care unit who underwent chest computed tomography (CT) scanning. A single attending radiologist reviewed the chest CT scans, and imaging features were recorded on a standardized form. Within 48 hours of chest CT scan, five sets of exhaled gas were sampled from the expiratory limb of the ventilator circuit. The gases were assayed with a commercially available electronic nose. Both linear and nonlinear analyses were performed to identify correlations between imaging features and the assayed gas signatures.** ***Results:*** **Twenty-five patients were identified, 13 of whom were diagnosed with pneumonia by CT scan. Support vector machine analysis was performed in two separate analyses. In the first analysis, in which a training set was identical to a prediction set, the accuracy of prediction results was greater than 91.6%. In the second analysis, in which the training set and the prediction set were different, the accuracy of prediction results was at least 80%, with higher accuracy depending on the specific parameters and models being used.** ***Conclusion:*** **The electronic nose is a new technology that continues to show promise as a potential diagnostic adjunct in the diagnosis of pneumonia and other infectious diseases.**

Key Words: **Pneumonia, biosensors, biosensing techniques, electronic nose, breath tests, smell.**
Laryngoscope, **114:1701–1705, 2004**

INTRODUCTION

Olfaction has been a part of physical diagnosis for centuries. This is evidenced by the terms *fetor oris* and *fetor hepaticus*. Use of olfaction in the modern physical examination has largely been lost because it is difficult both to qualify and to quantify. In the era of evidence-based medicine, data must be objective and findings must be reproducible by different examiners. Biological olfaction fits neither criterion.

Recent advances in polymer chemistry have led to the development and commercial availability of electronic nose technology. Although the specific technology used in different devices varies, archetypal electronic nose devices rely on chemical sensor arrays, pattern recognition algorithms, and complex statistical modeling.[1,2] Volatile "headspace" molecules are introduced into the devices, where they interact with the sensor array. Based on the reactivity of multiple sensors to the volatile molecules, a series of values are derived and the composite of these values generates an electronic signature for that odor.[3] The electronic signatures are mapped in multidimensional space and, based on the tightness of clustering of different signatures, odors can be grouped as "like" and "not like" using a variety of statistical models and pattern recognition algorithms.[4–7]

Electronic nose technology is potentially useful in clinical medicine because the devices are portable, testing is noninvasive, and results are rapid. In the diagnosis of pneumonia the electronic nose can be used to sample expired gases. If the device can be trained to recognize the electronic signature of the breath of patients with pneumonia, it can serve as diagnostic adjunct in the management of patients receiving mechanical ventilation.

There is currently no gold standard in the diagnosis of pneumonia. Pneumonia scoring systems, chest radiography, and bronchoscopy are all employed. In practice, diagnosis is based on the combination of available data

Presented as an Abstract at the Annual Meeting of the Triological Society, Phoenix, AZ, April 30, 2004.

From the Departments of Otorhinolaryngology—Head and Neck Surgery (N.G.H., E.R.T.), Radiology (D.T., W.T.M.), and Anesthesia (W.H.), University of Pennsylvania Health System, Philadelphia, Pennsylvania; and Cyrano Sciences (O.D.), Pasadena, California, U.S.A.

Editor's Note: This Manuscript was accepted for publication March 3, 2004.

Send Correspondence to C. William Hanson, MD, Department of Anesthesia, 5th Floor Founders, 3400 Spruce Street, University of Pennsylvania Health System, Philadelphia, PA 19104, U.S.A.

and clinical judgment. In the intensive care unit setting, critically ill patients often undergo chest computed tomography (CT) scanning to aid in diagnosis.

Previous work has demonstrated the ability of an electronic nose to distinguish among patients who were at low or high risk of ventilator-associated pneumonia and the ability of the electronic nose to identify different respiratory pathogens in vitro.[8,9] Based on these previous data, we hypothesized that the electronic nose could be used to detect exhaled volatile molecules from the breath of patients receiving mechanical ventilation and that the electronic nose signature could be correlated with the diagnosis of pneumonia by chest CT scan.

PATIENTS AND METHODS

After approval from the Institutional Review Board, 33 patients in the surgical intensive care units at the University of Pennsylvania Hospital who were receiving mechanical ventilation and were scheduled to undergo chest CT scan were identified. Patient exclusion criteria included hemodynamic instability, extubation immediately following CT scan, or request for exclusion by the patient or patient's family. Twenty-five sets of exhaled breath were acquired. Each set consisted of five samples of gas, which was collected from the expiratory limb of the ventilator circuit at the most proximal port. The gases were analyzed using the Cyranose 320, a commercially available electronic nose (Cyrano Sciences, Pasadena, CA), which was calibrated daily by sampling control vials of normal saline solution at 37°C. Daily calibration was performed to correct for potential sensor drift and to control for the effects of environmental and experimental variation. Identification of patients and sample acquisition were performed by a single physician.

The electronic nose used in the present study is handheld. It includes a small pump, a battery power source, microcircuitry, and a sensor array. Each sensor in the 32-sensor array consists of a carbon black/polymer composite, in which the carbon black creates conducting pathways through the polymer. As the specific polymer composite sensor interacts with the molecules in the sample volume, it swells to a variable degree, disrupting the carbon black conducting pathways and altering the electrical resistance of the sensor. The response of each particular sensor is a function of the characteristics of the polymers of which it consists. Sensor response curves were generated which demonstrated a positive deflection from baseline during sample acquisition (Fig. 1). Response curves with low signal-to-noise ratio or negative deflection were excluded.

All patients received mechanical ventilation with positive-pressure ventilation, using Puritan Bennett 7200 or 840 (Pleasanton, CA) ventilators. For the period of sample acquisition, "flow by" (used either as a trigger or primary mode) on the patient ventilator was suspended. Breath samples were obtained from an access port in the expiratory limb of the ventilator circuit just distal to the Y-shaped piece attached to the patient's endotracheal tube or tracheostomy tube within 48 hours of undergoing chest CT scan. If a heat and moisture exchange filter was in use, samples were obtained proximal to the filter. Before sampling the breath of each patient, the electronic nose was fitted with a clean Acrodisc CR 25-mm Syringe Filter (Pall, East Hills, NY). The filter-protected device was then connected to the access port in the ventilator circuit. Approximately 30 mL of expired air was sampled over a period of 30 seconds. Five consecutive samples were obtained. The sample information was downloaded from the electronic nose to a laptop computer for analysis.

The CT scans were read by a single attending radiologist. Thirty-three specific imaging features and the scanning sequences used were recorded on a standardized form (Fig. 2). Imaging feature results were recorded in a binary fashion as either positive or negative. To achieve statistical power, only imaging features with a large number of patients having and not having the feature can be compared. Because pneumothorax can be rapidly and inexpensively diagnosed by conventional chest radiography, we did not test the ability of the electronic nose to identify pneumothorax.

Principal component analysis was performed to determine whether there was clustering of gas sample data, based on imag-

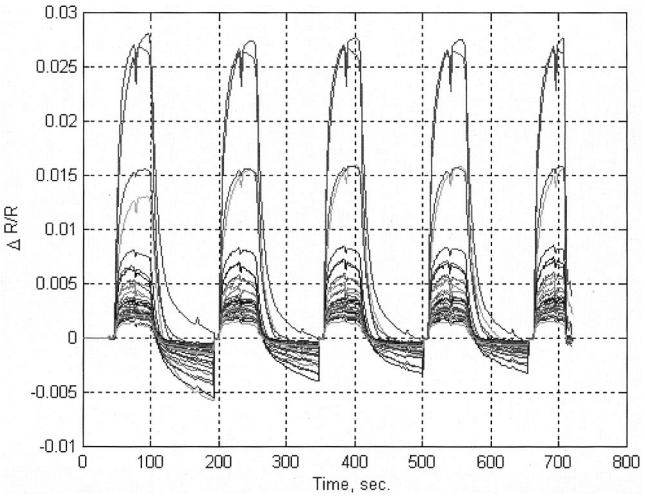

Fig. 1. Sensor response curve with a positive response and high signal-to-noise ratio. Δ R/R represents corrected sensor response from baseline after calibration with saline control samples. Each curve represents a different sensor.

Electronic Nose and CT Findings

MR# _____ Last Name _____ DOB _____ sex M F
Date of Exam _____

Interstitial Disease

Reticulation ___
Septal Lines ___
Bronchovascular ___
Cysts ___
Micronodules ___
Ground glass opacification ___
Honeycombing ___
Other interstital lung disease _____

Airway Disease Findings

Emphysema ___
Air Trapping ___
Tree in Bud ___
Bronchiectasis ___
Mucoid Impaction ___
Other Airway _____

Scanner Type

QXi
circle Sensation 4 (PT)
one Sensation 16
CT01
CTER
Slice Thickness ___
Recon. Interval ___
Contrast y / n

Mediastinal & Pleural Findings

Pneumothorax ___
Pleural Thickening ___
Pleural Effusion ___
Adenopathy ___
Mediastinal Mass ___
Pneumomediastinum ___
Mediastinal Collection ___
Acute pulmonary embolism ___
Pulmonary hypertension ___
Other Mediastinum _____

Alveolar Findings

Diffuse Consolidation ___
Congestive heart failure ___
Adult respiratory distress syndrome ___
Other diffuse alveolar lung disease _____

Focal Consolidation ___
Pneumonia ___
Atelectasis ___
Contusion ___
Infarct ___
Cavitary Lesion ___
Nodule ___
Mass ___
Nodule size ___
Other Focal Infiltrate _____

Fig. 2. Form used to record imaging features.

ing features identified. When there was clustering, support vector machine (SVM) analysis was performed in Matlab. Support vector machine analysis is a kernel-based, nonparametric method of neural computation and machine learning in which two flexible parameters are used to create a model for multidimensional function approximation. Our analysis was performed in two tiers. The first tier used identical training and prediction sets. This method of analysis is similar to an internal cross-validation approach. In SVM analysis the two flexible parameters are complexity and width. When the width is narrow, internal cross-validation yields high accuracy (100%) but external cross-validation yields low accuracy. As the width is increased, internal cross-validation accuracy generally decreases but the accuracy of the prediction set may increase.[7] In the second tier, the training set did not equal the prediction set. In this case, the data from the first three samples collected were used as the training set and the remaining two samples were used as the prediction set. This method of analysis is similar to an external cross-validation of the model.

RESULTS

Thirty-three patients were identified during the period of August to October 2003, who underwent chest CT scanning while receiving mechanical ventilation. Four patients were weaned from mechanical ventilation and extubated shortly after CT scan, precluding the opportunity for sample acquisition. The family of one patient asked that the patient not be included in the study. Two patients were hemodynamically unstable and thus were excluded from the study. In one patient the sensor response showed a negative deflection, probably as a result of sampling artifact, and the patient was excluded. The remaining 23 patients underwent 25 chest CT scans (21 patients had 1 scan and 2 patients had 2 scans). There were 13 male and 10 female patients; one man and one woman had two CT scans each. The average age was 63.7 ± 28.6 years. The admitting diagnoses are listed in Table I. The average time interval between CT scan and gas sample acquisition was 17.3 ± 14.5 hours.

Of the 25 CT scans reviewed, 13 of 25 demonstrated pneumonia and 12 of 25 revealed pneumothorax. Imaging features that were identified are listed in Table II. Based on this patient cohort, pneumonia was the only imaging feature that presented with a frequency appropriate for analysis. Initially, we had intended to test the ability of the electronic nose to identify patients with focal consolidation and atelectasis; however, nearly all patients included in the study demonstrated these findings. This was probably due to the high sensitivity of CT scan in identifying focal consolidation and atelectasis and the acuity of illness in the patient cohort.

Principal component analysis demonstrated clustering of data based on the diagnosis of pneumonia (Fig. 3). Because clustering was evident, SVM analysis was performed. The first tier of SVM analysis (internal cross-validation testing) demonstrated results of 91.6% to 100% accuracy (Table III). Figure 4 illustrates a two-dimensional view of the model. The second tier of SVM analysis (external cross-validation testing), as expected, was less accurate than the first tier because the training and prediction sets were different (Table IV and Fig. 5). The prediction set still demonstrated greater than 80% accuracy in predicting the CT scan results based on the electronic nose signature.

DISCUSSION

Gas chromatography and mass spectroscopy are able to identify particular molecules associated with disease, but for clinicians, knowledge of the molecules associated with infection is not clinically relevant; rather, identifica-

TABLE I.
Admitting Diagnoses.

Diagnosis	n
Bile leak (readmission following liver-kidney transplant)	1
Ascending aortic aneurysm	1
Aortic dissection	2
Tracheal tear (intubation injury)	1
Lung mass	1
Pneumonia (readmission following pneumonectomy)	1
Coronary artery disease (admitted for coronary artery bypass graft)	2
Motor vehicle crash (multiple orthopedic injuries)	4
Pancreatitis	2
Esophageal cancer	1
Motor vehicle crash (aortic dissection)	2
Colon cancer	2
Uterine cancer	1
Chronic lymphocytic leukemia	1
Small-bowel obstruction	1
Motor vehicle crash (closed-head injury)	1
Colovesicle fistula	1

TABLE II.
Imaging Features Identified.

Imaging Feature	n
Ground-glass opacification	2
Emphysema	5
"Tree in bud"	4
Bronchiectasis	1
Pneumothorax	12
Pleural thickening	1
Pleural effusion	21
Mediastinal adenopathy	1
Pneumomediastinum	1
Mediastinal collection	4
Acute pulmonary embolism	1
Pulmonary hypertension	1
Diffuse consolidation	4
Congestive heart failure	2
Adult respiratory distress syndrome	3
Focal consolidation	23
Pneumonia	13
Atelectasis	22
Pulmonary contusion	3
Pulmonary nodule	2

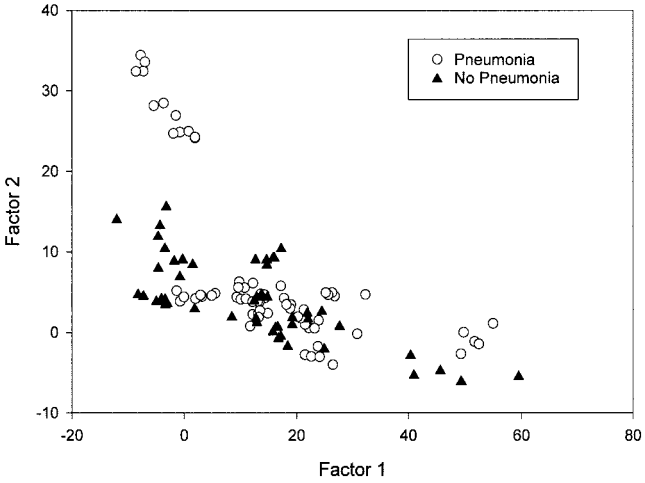

Fig. 3. Principal component analysis plots of patients with and without imaging features indicative of pneumonia. Factors 1 and 2 represent principal component vectors.

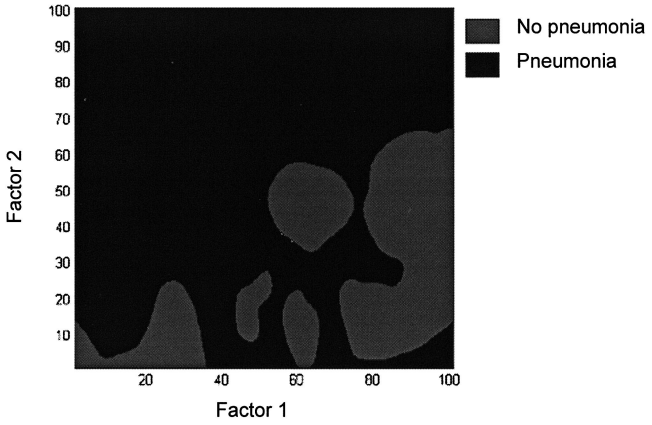

Fig. 4. Two-dimensional illustration of multidimensional SVM model using all samples in the training set. Parameters are complexity (c) = 10, width (w) = 5.

tion of the presence of infection or its absence is critical and can significantly alter patient management decisions. Gas chromatography and mass spectroscopy are also essentially nonportable devices and have not been applicable to bedside clinical use.

Electronic nose devices have emerged since the early 1990s and have demonstrated successful use in a variety of applications, including quality control for the food industry and applications in the defense and security industry, environmental monitoring, and health care.[3,10,11] Medical application of this technology relies on the association of volatile molecules with particular disease states. Recent studies using gas chromatography and mass spectroscopy have characterized some of these molecules.[12–15] In addition, the electronic nose has successfully identified several bacterial isolates in vitro.[9] An advantage of this technology is its ability to characterize odorants as "like" or "not like," without having to identify the particular molecules or pathogens associated with the disease. These devices can be trained to recognize disease entities based on physiological responses or the byproducts of these responses that are not entirely understood or specifically characterized. By accumulating a library of clinical data (index cases) and the associated vapor signatures, the electronic nose can be trained to identify clinical conditions without the need for the invasive studies or the multiple data points that were used in the diagnosis of the index cases. Testing is rapid and noninvasive and does not require significant training to perform.

Electronic nose technology has been studied in several medical settings, and its use in patients receiving mechanical ventilation has been promising.[2,16] Previous study using electronic nose technology demonstrated the potential to identify patients at high risk of pneumonia with correlation to an infection scoring system.[8] In the present study, we used the same electronic nose but correlated vapor signature data to chest CT scan readings. The second tier of SVM analysis demonstrated 80% accuracy in predicting the results of chest CT scans. With this small sample, the cause of the inability to predict the results of chest CT scan in 20% of cases is unclear. There are common characteristics of the exhaled breath of patients with pneumonia that the electronic nose is identifying, but these characteristics have not been enumerated with gas chromatography and mass spectroscopy. The breath of some patients with pneumonia may share these commonalities but may also contain other volatile chemicals, which significantly changes the vapor signature, resulting in incorrect predictions. Furthermore, the accuracy of chest CT imaging as a diagnostic tool for the detection of ventilator-associated pneumonia has not been adequately evaluated. There may be false-positive and false-negative diagnoses by chest CT imaging, which appear to be errors in classification by the electronic nose but in reality may be inaccurate diagnoses of the index cases. However,

TABLE III.
Support Vector Machine Analysis Prediction Results for Tier 1: Identical Training and Prediction Sets.

	No. of Correct Results (%)			
Analysis Model	C = 100, W = 0.5		C = 10, W = 5	
SVM	119/119	100	119/119	100
SVM + PCA (2)	119/119	100	109/119	91.6
SVM + PCA (3)	119/119	100	114/119	95.8

C = complexity; W = width; SVM = support vector machine; PCA = principal component analysis.

TABLE IV.
Support Vector Machine Analysis Prediction Results for Tier 2: Training and Prediction Sets Not Identical.

	No. of Correct Results (%)			
Analysis Model	C = 100, W = 0.5		C = 10, W = 5	
SVM	39/50	78	49/50	98
SVM + PCA (2)	37/50	74	40/50	80
SVM + PCA (3)	34/50	68	46/50	92

C = complexity; W = width; SVM = support vector machine; PCA = principal component analysis.

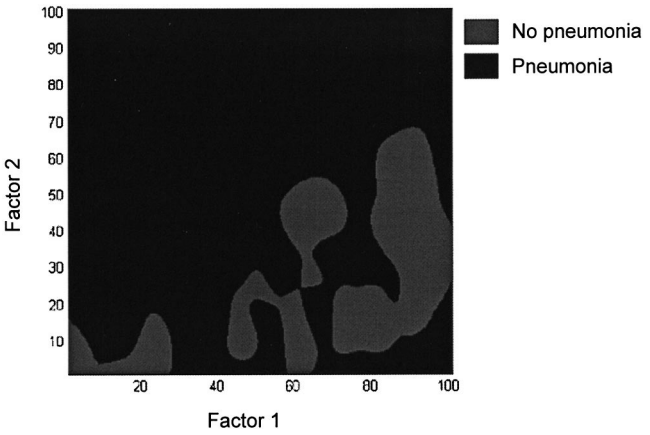

Fig. 5. Two-dimensional illustration of multidimensional support vector machine (SVM) analysis model using samples 1 to 3 in the training set. The remaining samples were used in the prediction set. Parameters are complexity (c) = 10, width (w) = 5.

there is not a gold standard test for ventilator-associated pneumonia with which the electronic nose could be trained.

CONCLUSION

Ventilator-associated pneumonia occurs in up to 25% of patients who have been receiving mechanical ventilation for more than 48 hours, and there is an association between ventilator-associated pneumonia and increased mortality.[17] There is no gold standard test in the diagnosis of ventilator-associated pneumonia. Several tests are used, including pneumonia scoring systems, which rely on multiple variables; bronchoscopy, which is invasive and may require sedation; and chest CT scanning, which requires transportation of critically ill patients.[18–21] A preferable alternative to any of these tests would be a univariate test with comparable sensitivity and specificity that could be used as a guide to treatment. We think the electronic nose can be a rapid, inexpensive, noninvasive test with the potential to, at least, duplicate, if not improve on, the diagnostic tools currently available.

The electronic nose is ideally suited to testing the breath of patients receiving mechanical ventilation, and the present study suggests that this technology has the potential to supplant other diagnostic alternatives. The demonstration of a correlation between chest CT scan diagnosis of pneumonia and the electronic nose sensor response indicates a potential clinical use as a noninvasive, univariate diagnostic adjunct for the diagnosis of ventilator-associated pneumonia. The signature generated by the electronic nose may serve as a threshold for the initiation of antibiotic therapy or may obviate the need for more invasive testing in certain patients. Further study of the use of this technology in the diagnosis of pneumonia and other disease processes involving the lungs and airways is warranted to determine its true diagnostic potential.

BIBLIOGRAPHY

1. Pearce TC. Computational parallels between the biological olfactory pathway and its analogue 'the electronic nose,' I: biological olfaction. *Biosystems* 1997;41:43–67.
2. Thaler ER, Kennedy DW, Hanson CW. Medical applications of electronic nose technology: a review of current status. *Am J Rhinol* 2002;15:291–295.
3. Nagle HT, Gutierrez-Osuna R, Schiffman SS. The how and why of electronic noses. *IEEE Spectrum* 1998;35:22–31.
4. Malthouse EC, Tahmane AC, Mah RSH. Nonlinear partial least squares. *Comput Chem Eng* 1997;21:875–890.
5. Wold S, Ruhe A, Wold H, Dunn WJ. The colinearity problem in linear regression: the partial lest squares (PLS) approach to generalized inverses. *SIAM J Scientific Stat Comput* 1984;5:735–743.
6. Boardman AE, Hui BS, Wold H. The partial least squares-fix point method of estimating interdependent systems with latent variables. *Commun Stat Theory Methods* 1981; A10(7):613–639.
7. Back AD. Classification using support vector machines. Riken Brain Science Institute, Wako-shi, Japan. Available on the Web at: http://andrewback.com/webpapers/svm/index.php. Accessed December 16, 2003.
8. Hanson CW, Steinberger HA. The use of a novel electronic nose to determine the etiology of intrapulmonary infection. *Anesthesiology* 1997;87:A269.
9. Lai SY, Deffenderfer OF, Hanson W, Phillips MP, Thaler ER. Identification of upper respiratory bacterial pathogens with the electronic nose. *Laryngoscope* 2002;112:975–979.
10. Polakoff PL. Medical breath analysis discovers telltale proof of toxic exposures. *Occup Health Safety* 1993;62:20, 22.
11. Pierce TC, Schiffman SS, Nagel HT, et al. *Handbook of Machine Olfaction: Electronic Nose Technology*. Weinheim, Germany: Wiley-VCH, 2003.
12. Podebrad F, Heil M, Reichert S, et al. 4,5-dimethyl-3-hydroxy-2[5h]-furanone (sotolone): the odour of maple syrup urine disease. *J Inherit Metab Dis* 1999;22:107–114.
13. Phillips M, Sabas M, Greenberg J. Increased pentane and carbon disulfide in the breath of patients with schizophrenia. *J Clin Pathol* 1993;46:861–864.
14. Pavlou AK, Magan N, Sharp D, et al. An intelligent rapid odour recognition model in discrimination of Helicobacter pylori and other gastroesophageal isolates in vitro. *Biosensors Bioelectronics* 2000;15:333–342.
15. Caspary WF, Schaffer J. 14C-D-galactose breath test for evaluation of liver function in patients with chronic liver disease. *Digestion* 1978;17:410–418.
16. Thaler ER. The diagnostic utility of an electronic nose: rhinologic applications. *Laryngoscope* 2002;112:1533–1542.
17. Morehead RS, Pinto SJ. Ventilator-associated pneumonia. *Arch Intern Med* 2000;160:1926–1936.
18. Pugin J, Auckenthaler R, Mili N, Janssens JP, et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991; 143(5, Pt 1):1121–1129.
19. A'Court CH, Garrard CS, Crook D, et al. Microbiological lung surveillance in mechanically ventilated patients, using non-directed bronchial lavage and quantitative culture. *Q J Med* 1993;86:635–648.
20. Winer-Muram HT, Rubin SA, Ellis JV, et al. Pneumonia and ARDS in patients receiving mechanical ventilation: diagnostic accuracy of chest radiography. *Radiology* 1993;188: 479–485.
21. Winer-Muram HT, Steiner RM, Gurney JW, et al. Ventilator-associated pneumonia in patients with adult respiratory distress syndrome: CT evaluation. *Radiology* 1998;208: 193–199.

Editor's Note

Footnote: The electronic nose device used in this study is a research tool and has not been approved for clinical use.