Use of an Electronic Nose to Distinguish Cerebrospinal Fluid From Serum

Erica R. Thaler, MD; Francisca C. Bruney, David W. Kennedy, MD; C. William Hanson, MD

Background: Efforts to mimic the biologic olfactory system have resulted in the development of an electronic nose, whereby volatile gases may be identified by means of organic semiconductors. Such devices have been used in the food and beverage industry for quality-control purposes, but to date have not been used in the field of medicine.

Objective: To present the application of an electronic nose for clinical decision making by assessing the ability of an electronic nose to distinguish cerebrospinal fluid (CSF) from serum.

Design: Randomized, prospective, masked study.

Subjects: Nineteen matched sets of CSF and serum from inpatients at a university hospital.

Results: The electronic nose was able to distinguish CSF from serum in 18 of 19 patients. The data points for 18 of 19 CSF and 18 of 19 serum samples were within statistically distinct cluster groups, suggesting that the device is able to identify an unknown sample as CSF or serum.

Conclusions: This new technology is able to distinguish CSF from serum with a high degree of accuracy and speed, and with small sample quantity, potentially allowing the physician to identify reliably CSF otorrhea or rhinorrhea. This revolutionary diagnostic approach may have further, widespread application in the field of otorhinolaryngology and in medicine as a whole.

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The human sense of smell has been little utilized in modern medicine because of its lack of precision. However, other species such as dogs, with highly adapted olfactory systems, have legendary abilities to distinguish odor, and have even been used for diagnostic purposes in medicine. Efforts to artificially reproduce biologic olfactory systems have resulted in several technologies that are capable of analyzing odor with remarkable precision.

Several technologies are used in electronic noses. The first kind of sensors that were developed were the metal-oxide semiconductors, which measure the change in conductivity at a catalytic surface when gas molecules decompose at high temperatures. There are several types of mass-dependent electronic noses, such as quartz-crystal microbalances and surface acoustic wave devices, which measure a change in sensor mass as gas molecules are adsorbed. Optical-based sensors, eg, glass fibers coated with solvatochromic dyes, measure the change in fluorescence as gas molecules interact with the dye. In other sensors, conductivity changes as a gas diffuses into a polymer. Conducting polymers are organic semiconductors with a backbone in which single and double bonds alternate, giving rise to a large delocalized electron cloud. The polymers interact with volatile molecules (in odors) by changing conductance. Different polymers can be designed to respond preferentially to specific stereochemical characteristics of the odorant (eg, alcohols, ketones). Neural networks and principle component analysis are commonly used to identify and distinguish odors from one another with each of these technologies.

Electronic nose technology has been used in the food and beverage industries, to identify spoilage, and by NASA (National Aeronautics and Space Administration), to identify noxious gases. One application in the field of medicine has been to distinguish patients with pneumonia from control subjects by analyzing exhaled gases.1

The differentiation of cerebrospinal fluid (CSF) from mucous or serum is of critical importance in managing patients with potential CSF otorrhea or rhinor-
MATERIALS AND METHODS

After obtaining institutional review board approval, matched sets of CSF and serum were obtained from the Pepper Laboratory of the University of Pennsylvania Medical Center in Philadelphia. The study was prospective, randomized, and masked in that no information regarding the patients was known prior to analyzing the samples, and samples were obtained based only on availability of matched sets on several different test days. The samples used were excess fluid to be otherwise discarded after all necessary clinical testing had been accomplished.

Samples of CSF and serum of 0.1 to 0.2 mL each were vaporized and analyzed by an organic semiconductor-based electronic nose (Osmetech, Hollis, NH). This device consists of a 32-element array of conducting polymers with differing responsiveness to various chemical species. Odor analysis was performed by passing the vaporized gas sample over the conductor array (Figure 1). The response of the sensor array to a sample gas is represented as a point in a 32-dimensional space (the relative amplitude of response of each of the 32 sensors to a sample odor). Principle component analysis was then used to depict odors on a 2-dimensional graph. Statistical analysis was assessed using the Mahalanobis distance, a measure of class separation between different cluster centroids. A value greater than 8 indicates distinct classes.

RESULTS

A total of 19 matched sets of CSF and serum were analyzed by the electronic nose. Results were available in 90 seconds. The specimens were run in 2 separate batches. The first, with 6 samples, was run manually, and the second, with 13 samples, was run on an automated version of the device because after the first run that a difference between substances was identifiable (Figure 2 and Figure 3). Eighteen of 19 patients’ CSF specimens were graphically distinct and separate from their serum specimens. Furthermore, 18 of 19 CSF specimens and 18 of 19 serum specimens mapped out graphically in clusters, with CSF and serum reliably falling in distinct locations. The Mahalanobis distance for the first batch was 7.5, due to the one overlapping sample. Excluding that data point, the Mahalanobis distance was 20.

For the second batch, this distance was 16. These results indicate statistical significance. Laboratory data available for patients’ CSF and serum samples were then retrospectively reviewed, to de-
termine if there were any distinct features discernible through their routine laboratory testing (Table 1 and Table 2). No trends were identified, including in the 1 patient for whom the 2 specimens did not appear to fall within the range of the others.

**COMMENT**

These early data demonstrate that an electronic nose is able to distinguish CSF from serum rapidly, reliably, and with small sample quantity. Such a testing device, made clinically available, could provide useful real-time analysis for medical decision making in patients with suspected CSF rhinorrhea or otorrhea. The small amount of material necessary for testing and the speed with which it is accomplished represent improvements over the current standard of care, a test for presence of $\beta_2$ transferrin.

The one patient whose specimens fell outside the representative data clusters for both serum and CSF did not have any identified abnormalities on available testing. There are several possible explanations for this outcome. It is possible that the specimens were contaminated or “overwhelmed” by a stronger scent than those typically picked up by the electronic nose. A systemic disorder productive of a high level of nitrogen might be one such explanatory overwhelming scent. It is also possible that the aberrance simply represents a technical error of the device. More data must be accumulated before this can be interpreted further.

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Table 1. Cerebrospinal Fluid (CSF) and Serum Data for Patients in Figure 2 (Manual)

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>CSF Results</th>
<th>Serum Results (Panel 6)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Protein, mg/dL</td>
<td>Glucose, mmol/L</td>
<td>Culture</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>3.6</td>
<td>Not available</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>2.8</td>
<td>No growth</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>3.6</td>
<td>No growth</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>2.9</td>
<td>No growth</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>9.2</td>
<td>No growth</td>
</tr>
<tr>
<td>6</td>
<td>109</td>
<td>8.7</td>
<td>No growth</td>
</tr>
</tbody>
</table>

*To convert glucose to milligrams per deciliter, divide millimoles per liter by 0.05551; to convert creatinine to milligrams per deciliter, divide micromoles per liter by 88.4.*
CONCLUSIONS

The electronic nose appears to be able to distinguish CSF from serum rapidly and with small sample quantity. This device may have potential clinical use in the management of patients with suspected CSF rhinorrhea. The current technology simply requires collection of a 0.1- to 0.2-mL aliquot of suspected rhinorrhea as well as a control serum sample. These samples are analyzed with the electronic nose and compared with previous cluster groups for purposes of identification. The device theoretically has the capability of identifying samples of smaller size, collected on swabs or pledgets, although these sorts of specimens have not yet been studied. Further work is in progress to assess the reliability of the device using these other techniques.

The device has the potential for further applications in otorhinolaryngology. These include intraoperative identification of perilymph in exploring for oval or round window fistula, rapid identification of CSF leak during skull base procedures, and following post-traumatic CSF leaks as they heal without operative intervention. The device may also be able to identify the presence of bacteria in a specimen, thereby permitting real-time evaluation for the presence of ongoing infection.

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Reprints: Erica R. Thaler, MD, Department of Otorhinolaryngology, 5 Silverstein, 3400 Spruce St, Philadelphia, PA 19104 (e-mail: thaler@mail.med.upenn.edu).

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