Measurement of brain tissue oxygenation performed using positron emission tomography scanning to validate a novel monitoring method


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Object. The benefits of measuring cerebral oxygenation in patients with brain injury are well accepted; however, jugular bulb oximetry, which is currently the most popular monitoring technique used has several shortcomings. The goal of this study was to validate the use of a new multiparameter sensor that measures brain tissue oxygenation and metabolism (Neurotrend) by comparing it with positron emission tomography (PET) scanning.

Methods. A Neurotrend sensor was inserted into the frontal region of the brain in 19 patients admitted to the neurointensive care unit. After a period of stabilization, the patients were transferred to the PET scanner suite where C15 O, 15 O2, and H15 O PET scans were obtained to facilitate calculation of regional cerebral blood volume, O2 metabolism, blood flow, and O2 extraction fraction (OEF). Patients were given hyperventilation therapy to decrease arterial CO2 by approximately 1 kPa (7.5 mm Hg) and the same sequence of PET scans was repeated. For each scanning sequence, end-capillary O2 tension (PvO2) was calculated from the OEF and compared with the reading of brain tissue O2 pressure (PbO2) provided by the sensor.

In three patients the sensor was inserted into areas of contusion and these patients were eliminated from the analysis. In the subset of 16 patients in whom the sensor was placed in healthy brain, no correlation was found between the absolute values of PbO2 and PvO2 (r = 0.2, p = 0.29); however a significant correlation was obtained between the change in PbO2 (ΔPbO2) and the change in PvO2 (ΔPvO2) produced by hyperventilation in a 20-mm region of interest around the sensor (p = 0.78, p = 0.0035).

Conclusions. The lack of correlation between the absolute values of PbO2 and PvO2 indicates that PbO2 cannot be used as a substitute for PvO2. Nevertheless, the positive correlation between ΔPbO2 and ΔPvO2 when the sensor had been inserted into healthy brain suggests that tissue PO2 monitoring may provide a useful tool to assess the effect of therapeutic interventions in brain injury.

Key Words • severe brain injury • cerebral monitoring • brain tissue oxygenation • validation • positron emission tomography

Abbreviations used in this paper: CBF = cerebral blood flow; CBV = cerebral blood volume; CMRO2 = cerebral metabolic rate of O2; CT = computerized tomography; ΔPbO2 = change in pressure of O2 in brain tissue; ΔPvO2 = change in pressure of O2 in vein; OEF = O2 extraction fraction; PET = positron emission tomography; ROI = region of interest; SjvO2 = saturation of jugular venous O2; SO2 = saturation of O2.
a sensor that can be used to measure O₂ tension, CO₂ tension, pH, and temperature of brain tissue (Neurotrend). Predictable changes in PbO₂, PCO₂, and pH in brain tissue in response to physiological challenges have been demonstrated in animal models, in which similar sensors have been tested.

There is now considerable interest worldwide in the use of these sensors in the treatment of brain-injured patients in the intensive care unit to help minimize the occurrence of ischemia during intracranial aneurysm surgery and in the treatment of patients with acute stroke. The physical accuracy of these sensors has been validated when used in arterial blood; however, there is still little understanding of how tissue PbO₂ readings obtained from our sensor relate to other well-established indices of regional cerebral oxygenation. It is essential that the sensor be validated against such established methods. Validation against conventional oximetry is hampered by the failure of jugular bulb oximetry to address the regional monitoring capabilities of the new device. We have therefore assessed the Neurotrend sensor against the gold standard of PET scanning, which has been used to provide regional end-capillary O₂ tensions (PvO₂) for reference.

The aim of this study was to validate readings provided by the Neurotrend sensor by comparing absolute values and changes in the values of PbO₂ with those of PvO₂ derived from triple ¹⁵O PET scanning after medical intervention with hyperventilation therapy.

Clinical Material and Methods

Patient Population

With the approval of the Local Research Ethics Committee and the United Kingdom Radiation Protection Committee, and written consent from the patients’ relatives, 19 patients admitted to our neurological intensive care unit with severe head injury or a poor-grade subarachnoid hemorrhage were studied. All patients had been determined to have a Glasgow Coma Scale score of 8 or less. The patients were sedated and received mechanically assisted ventilation. The treatment of these patients was based on protocols established for our neurological intensive care unit.

Monitoring of Physiological Parameters

In all patients routine invasive monitoring was applied to obtain measurements of mean arterial blood pressure, central venous pressure, and intracranial pressure, as well as continuous jugular bulb oximetry (measurement of SjvO₂). In addition, multiparameter sensors were used to measure brain and arterial O₂, CO₂, pH, and temperature. After a three-point calibration had been performed using precision gases, two sensors, Neurotrend and Paratrend 7, were inserted into each patient. The Paratrend 7 sensor was inserted through an 18-gauge cannula into a femoral artery for continuous blood gas analysis. The Neurotrend was inserted into brain tissue through a specially designed bolt that was placed in the frontal region of the skull. The position of the sensor was confirmed by a CT scan obtained after sensor placement. After a period of stabilization, the patients were transferred to the suite housing the PET scanner, where their intensive care was continued.

Protocol for PET Scanning

Once patients were positioned in the PET scanner and all monitoring devices had been reconnected, transmission scanning was performed to correct subsequent emission scans for photon attenuation. Following transmission scanning, a baseline carboxyhemoglobin level was obtained from arterial blood and the patients were given 300 MBq of inhaled C¹⁵O over a 45-second period. Data were acquired over a single 5-minute frame between 1 and 6 minutes post inhalation, thereby providing information regarding regional CBV. Only trace amounts of C¹⁵O were administered, and the procedure caused no rise in carboxyhemoglobin levels in any of the patients studied.

To measure the CMRO₂ by using the steady-state technique, 7200 MBq of ¹⁸O₂ was administered at a constant rate and emission data were acquired in two 5-minute frames following a build-up period of 10 minutes. To obtain regional CBF by using the steady-state technique, data were acquired during the infusion of 800 MBq of H₂¹⁵O, in two 5-minute frames following a 10-minute build up to steady state.

During the time baseline C¹⁵O, ¹⁸O₂, and H₂¹⁵O scans were being acquired, inspired O₂ concentrations and arterial CO₂ tensions were kept constant. As soon as the H₂¹⁵O sequence had been completed, minute ventilation was increased to reduce arterial CO₂ by approximately 1 kPa (7.5 mm Hg) within 5 minutes. If the SjvO₂ had decreased below 55%, hyperventilation would have been limited or abandoned, although this did not occur in the present study. Once the arterial CO₂ had stabilized, the same scanning sequences were repeated, except in reverse order.

Neurotrend Protocol

Recordings of mean arterial blood pressure, intracranial pressure, SjvO₂, and arterial blood gas levels (the last obtained with the aid of the Paratrend 7), as well as brain tissue tension of gases and temperature (Neurotrend) were made at least twice during each phase of scanning.

Analysis of PET Data

The position of the sensor was determined on the basis of findings on the CT scan and ROIs were drawn around the sensor on the appropriate slices of each PET scan. A preliminary assessment revealed that a 20-mm-diameter ROI provided the best compromise between an acceptable ROI signal-to-noise ratio and the need to limit the ROI to tissue immediately surrounding the sensor. The ROI data obtained from the C¹⁵O, ¹⁸O₂, and H₂¹⁵O PET scans were input into standard kinetic models to produce ROI values of CBV, CBF, CMRO₂, and OEF.

Calculation of PvO₂

The PvO₂ values were calculated using two equations provided by Kelman. The first step involved the determination of the PvO₂ under standard conditions through iterative solution of the following equation, which accurately relates SO₂ to standard PO₂ for a PO₂ greater than 1 kPa (7.5 mm Hg): SO₂ = 100 × (a₁p + ap + a₃p² + a₄p³ + p⁴)/(a₀ + a₁p + a₂p² + a₃p³ + p⁴), where SO₂ = arterial SO₂ × (1 - OEF), p denotes PvO₂ under standard conditions, and each aᵢ is a fixed constant.
Validation of brain tissue PO$_2$ by using PET scanning

The second equation converts PvO$_2$ under standard conditions to PbO$_2$ at the patient’s temperature, brain PCO$_2$, and jugular venous pH, in millimeters of mercury: \[ \text{PvO}_2 = \text{PbO}_2 \left( \frac{37 + 0.06\text{log PCO}_2}{37 + 0.06\text{log PCO}_2} \right) \] The derived value of PvO$_2$ was calculated at normocapnia and hypocapnia in each patient and compared with the measured values of PbO$_2$.

**Statistical Analysis**

Data were analyzed using commercially available software. The data were assessed for normality of distribution by using the Kolmogorov–Smirnov test. Baseline values of PbO$_2$ and PvO$_2$ were found to be normally distributed and were assessed using linear regression analysis. Changes in PbO$_2$, however, were not normally distributed and were therefore compared with changes in PbO$_2$ by using the Spearman rank correlation coefficient. Similarly, changes in CBF obtained from PET scans were compared with changes in PbO$_2$ and PvO$_2$.

A Bland–Altman plot was constructed in which the sum of the mean PbO$_2$ and mean PvO$_2$ was compared with the difference between these values (PvO$_2$ - PbO$_2$).

**Sources of Supplies and Equipment**

The Neurotrend and Paratrend 7 sensors were obtained from Diametrics Medical (High Wycombe, Buckinghamshire, UK), Codman and Shurtleff, Inc. (Raynham, MA), which now distributes the Neurotrend sensor in the United States, provided equipment for routine invasive monitoring of intracranial pressure. The equipment used to monitor SjvO$_2$ was acquired from Baxter Healthcare (Newbury, Berkshire, UK). General Electric Medical Systems (Milwaukee, WI) manufactured the Advance PET scanner. Statistical analysis was performed using Statview version 4.5 software, obtained from SAS Institute, Inc. (Cary, NC).

**Results**

**Study Group**

Of the 19 patients studied, 17 were admitted with traumatic brain injury and two were admitted after experiencing subarachnoid hemorrhage from a ruptured aneurysm. Thirteen patients were male and six were female. The mean age ± standard deviation of the patients was 35 ± 17 years.

**Sensor Placement**

There were no complications associated with sensor insertion in these patients. A review of CT scans revealed that the tip of the sensor was located in healthy brain white matter in 16 patients and in injured brain tissue (contusion or pericontusional areas) in three patients. Analysis was performed in all 19 patients and also separately in the 16 patients in whom the sensor had been placed in healthy brain. Three sensors displayed very low readings (PbO$_2$ < 0.4 mm Hg) after insertion; in only one of these cases had the sensor been inserted into injured brain. All three of these sensors did respond to hyperventilation. One additional sensor failed to respond to hyperventilation therapy during the study.

**Comparison of PbO$_2$ and PvO$_2$**

Analysis of all 19 patients showed no significant correlation between PbO$_2$ and PvO$_2$ (r = 0.12, p = 0.7) when the data were pooled. The correlation remained insignificant in the subset of 16 patients in whom the sensor had been inserted into healthy brain (r = 0.2, p = 0.29). Figure 1 represents the correlation between PbO$_2$ and PvO$_2$ during normocapnia in all 19 patients (three patients in whom the sensor was inserted into injured areas of the brain [gray dots] and 16 in whom it was inserted into healthy brain [black dots]). The line indicates the mean value of PvO$_2$ in healthy brain according to the study by Leenders, et al.

When the ΔPbO$_2$ and ΔPvO$_2$ were analyzed in all 19 patients, the data still showed no significant correlation (Spearman rank ρ = 0.28, p = 0.24). In the subset of 16 patients in whom the sensor had been placed in healthy brain, however, a highly significant correlation was obtained between ΔPbO$_2$ and ΔPvO$_2$ (Spearman rank ρ = 0.78, p = 0.0035). Figure 2 demonstrates the correlation between ΔPbO$_2$ and ΔPvO$_2$ in the 16 patients in whom the sensor had been placed in healthy brain with the addition of the three patients in whom the sensor had been placed in injured brain.

The correlation between changes in CBF and PbO$_2$ was not statistically significant (Spearman rank ρ = 0.5, p = 0.06). In the correlation between changes in CBF and PbO$_2$, the ρ value was 0.43, and the probability value was 0.01.

**Discussion**

Measurement of PbO$_2$ has been attempted for many
years. Sensors incorporating the Clark type of electrode into a multiparameter sensor (Paratrend 7) have been evaluated in animal studies and have demonstrated stable and reproducible readings in tissue O₂ tension with predictable responses to physiological changes. These findings have been supported by findings of clinical studies conducted by several groups. We have previously shown that changes in physiology result in different responses in oxygenation in healthy and injured areas of the brain. With this in mind, we analyzed data obtained in the 16 patients in whom the sensor had been placed in healthy brain, and the three patients in whom the sensor had been placed in injured brain were excluded from that analysis.

Principle of Validation With PET Scanning

The advantage of PET scanning is that it provides non-invasive, quantitative data on global and regional CBF, CBV, CMRO₂, and OEF. The availability of regional OEF measurements allows the calculation of regional end capillary PvO₂. Because PET scanning is the only method available to measure regional OEF at present, it is regarded as the gold standard in comparisons of methods of measuring cerebral oxygenation. Although PET studies reveal marked regional heterogeneity in OEF values across the injured brain, the values of OEF that we obtained from regions of healthy brain in our study are similar to those reported by Leenders, et al., in studies of healthy volunteers. Using a methodology similar to that used in this study, Alpert and colleagues published a mean value of PvO₂ of 31.2 mm Hg in healthy volunteers—the same value as the mean PvO₂ recorded in our study during normocapnia, which was 31.1 mm Hg.

Comparison of PvO₂ and PbO₂

The values of PbO₂ were different from the derived values of PvO₂ in all cases, with the value of PvO₂ higher in all but one patient. This observation can be explained by considering the locations from which the two forms of data are measured. The PvO₂ is a measurement of O₂ tension in the end capillary, whereas PbO₂ is a measurement of tissue O₂ tension averaged over a volume of tissue that is still undetermined, but is likely to be a few cubic millimeters in size and contain extracellular fluid, capillaries, cells, and axons. The value of PbO₂ obtained from such a volume of tissue is, therefore, unlikely to be the same as the O₂ tension of the end capillary. The difference between the values of PbO₂ and PvO₂ is likely to depend on factors such as diffusion distance and diffusion gradients. The diffusion distance may be increased as a result of physiological changes such as cellular swelling or microscopic arteriovenous shunts directing flow away from the capillaries. The finding of a higher value of PvO₂ than that of PbO₂ is consistent with these physiological effects. Furthermore, the interface between capillary and site of PbO₂ measurement will be different in each patient and will therefore demonstrate interindividual variation. This would account for the lack of correlation between PvO₂ and PbO₂ values when all patients were grouped.

Figure 3 shows a classic Bland–Altman plot, which demonstrates greater variability in measured values at lower values of tissue O₂ tension. This could be explained by a lower signal-to-noise ratio from the PET scans at low PvO₂ values or by less accurate readings from the Neurotrend sensor at low PbO₂ values. If it is the sensor that is the cause of these inaccuracies, changes in calibration at these low values will help improve the accuracy of the readings.

The ΔPvO₂ and ΔPbO₂ in response to hyperventilation therapy, however, reflect changes in brain physiology in response to an identical challenge; although such changes may not be identical, they would be expected to show similar trends. It is not surprising, therefore, that these figures displayed a significant correlation. In addition, our previous demonstration of varying physiological responses in healthy and injured brain explains the restriction of such a correlation to situations in which the sensor was situated in nonlesioned areas. This would imply that the trends of the PbO₂ demonstrated by the Neurotrend sensor reflect those of changes in PvO₂ derived from PET scanning.
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In three patients the values of \( \text{PbO}_2 \) were very low during states of both normocapnia and hypocapnia. Although sensor failure was possible, this was excluded by demonstration of normal function after the sensor was removed from the patient. There are other explanations for these findings. First, the sensor may have been inserted into an area of contusion in which there was a poor blood supply. This was the case in one of these patients. Alternatively, the area surrounding the sensor may have been diffusely swollen, thereby providing a large diffusion distance and causing a low \( \text{PbO}_2 \). Third, microhemorrhages, which may have occurred along the probe track after insertion, may surround the sensor. These microhemorrhages, which can only be detected by histological examination, have been reported as being responsible for low readings of \( \text{PbO}_2 \) in animal models.\(^{20}\)

**Clinical Utility**

The rationale for monitoring cerebral oxygenation in patients suffering from acute brain injury is widely accepted. Any new monitoring method has to be compared not only with a gold standard (in this study PET scanning), but also against existing techniques. The most common method in current use is jugular bulb oximetry (measurement of \( \text{SjO}_2 \)), which can provide information regarding global cerebral oxygenation. We have demonstrated in a previous study, however, that sensors used to measure \( \text{O}_2 \) tension in brain tissue detect changes in regional brain oxygenation, which would otherwise be missed by measuring \( \text{SjO}_2 \).\(^{4}\) Although absolute values of \( \text{PbO}_2 \) may not reflect those of \( \text{PvO}_2 \), changes in \( \text{PbO}_2 \) do reflect the physiological changes in a focal area of tissue. Furthermore, the correlation of changes in \( \text{CBF} \) to changes in \( \text{PbO}_2 \) is more significant than that of changes in \( \text{CBF} \) and \( \text{PvO}_2 \). This would support the use of brain tissue \( \text{O}_2 \) sensors in the clinical setting as a device for monitoring trends in cerebral oxygenation, but the technology is not yet robust enough to base therapeutic decisions on absolute values.

As with any monitor, it is the ability to demonstrate continuous trends that are clinically useful. Continuous monitoring of \( \text{SjO}_2 \) is associated with a number of technical difficulties, and a large proportion of data points (approximately 50%)\(^{18}\) obtained using this technique may be difficult to interpret due to artifacts (such as those produced by contact with the wall of the jugular vein). In such situations, or in settings in which jugular oximetry is inappropriate (for example, in cases of arteriovenous malformations or jugular thrombosis), tissue monitoring can provide a useful means of assessing the effects of interventions (such as hyperventilation therapy) on healthy brain tissue.

**Conclusions**

The Neurotrend sensor is now used in many centers around the world for monitoring patients with brain injury and it is important that its strengths and weaknesses be delineated. Clearly, our results indicate that the information obtained using the Neurotrend sensor does not reflect the \( \text{O}_2 \) content of end capillaries as measured by PET scanning. It is possible, however, that the sensor provides data regarding a different, discrete, and, possibly, physiologically relevant tissue compartment. In contrast with the lack of correlation between \( \text{PbO}_2 \) and \( \text{PvO}_2 \), we found a useful relationship between changes in cerebral oxygenation as measured by PET scanning and the Neurotrend sensor. Although the precise significance of absolute \( \text{PbO}_2 \) values measured using the Neurotrend sensor requires further study, it appears clear that when the sensor is inserted into healthy brain, it can be used as a continuous and robust device for assessing the effect of therapeutic interventions on cerebral oxygenation.

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**References**


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