Monitoring of autoregulation using laser Doppler flowmetry in patients with head injury

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The essence of head injury management is the provision of optimum conditions for recovery from damage already sustained and the avoidance of development of secondary brain injury. Cerebral ischemia is an important cause of secondary brain insult that can affect outcome in the head-injured patient. Maintenance of adequate cerebral perfusion pressure (CPP) is important in preventing cerebral ischemia and even improves the function of ischemic brain tissue. The normal human cerebral circulation has the ability to maintain a stable cerebral blood flow (CBF) over a wide range of CPPs. This ability, called autoregulation of CBF, may be impaired in the injured brain. The loss of autoregulation renders the brain more susceptible to systemic insults, such as derangement of blood pressure.

The success of the various strategies for CPP management depends on the accurate determination of the status of autoregulation. Moreover, the autoregulatory status may vary with time as patients deteriorate or recover, hence the need for continuous assessment of autoregulation. However, there is a paucity of satisfactory methods for this assessment. Determination of autoregulation status requires a measurement of relative changes in CBF when CPP changes. Laser Doppler flowmetry (LDF) offers this facility, albeit only in one small area of the brain. A pilot study demonstrated the feasibility of the technique as well as the lower limit of autoregulation, but a larger study is required to determine whether the autoregulatory status determined from the relationship between LDF and CPP is a predictor of outcome.

The authors studied 31 comatose head-injured patients to assess the clinical usefulness of laser Doppler flowmetry (LDF) in continuous autoregulation monitoring. The LDF probes were placed on the surface of the cerebral cortex. Data on LDF, intracranial pressure (ICP), and arterial blood pressure (ABP) were recorded and continuously entered into a computer. The data were broken down into multiple segments of 15 minutes' duration (epochs). Epochs showing rapid change in cerebral perfusion pressure (CPP), change in CPP of less than 10 mm Hg, LDF values of less than five arbitrary units, and loss of ABP/ICP waveform were excluded from further analysis. A linear relationship between LDF and CPP in individual epochs was used as an indicator of loss of autoregulation.

The relationship between LDF and CPP changed with time, indicating improvement or deterioration in autoregulation. Longitudinal analysis of all the epochs measured in a patient revealed three patterns of progress: 1) intact autoregulation; 2) transient loss; and 3) persistent loss of autoregulation. All five patients with intact autoregulation had a good outcome. Ten patients experienced transient loss of autoregulation; of these four had a good outcome, five were moderately disabled, and one was severely disabled. Transient impairment of autoregulation did not always indicate poor outcome, provided the impaired autoregulation responded to treatment. In 11 patients who had persistent loss of autoregulation, nine died and two were severely disabled. In five cases the LDF probe lost contact with the cerebral cortex and no useful information was obtained. Real-time measurement of autoregulation using LDF and CPP monitors was achieved and the findings were related to outcome in these patients.

Key Words • laser Doppler flowmetry • head injury • autoregulation • cerebral perfusion pressure
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traumatic intracerebral hemorrhage and required neurosurgery to evacuate mass lesions or for monitoring of intracranial pressure (ICP). Patients were managed according to a standard protocol, regardless of the LDF result. The patients’ ages ranged from 5 to 65 years. The admission Glasgow Coma Scale (GCS) scores ranged from 3 to 14. Patients were monitored from the first operation until they were weaned from the ventilator, and their outcome was determined at 6 months according to the Glasgow Outcome Scale (GOS). Pathological appearance on computerized tomography (CT) scan was classified as described in the report from the National Institutes of Health Traumatic Coma Data Bank.11

Technique of LDF Monitoring

We used an LDF monitor (model BPM2; Viasamedics Inc., St. Paul, MN) that incorporates a low-power solid-state laser diode as the source of coherent light. The laser emits an infrared light (760–800 nm wavelength) that is directed to the tissue by means of an optical fiber and a disk-shaped probe. The probe was sterilized by immersion in 2% glutaraldehyde solution for 30 minutes with subsequent washing in sterile saline. The disk is oval with a diameter of 10 mm and a thickness of 1 mm, and a long optical fiber connects the probe with the monitor. For patients requiring craniotomy, the probe was placed in the subdural space over the relatively normal cerebral cortex on the side containing major injuries. For patients with diffuse brain injury who required ICP monitoring, the LDF probe was inserted into the subdural space through an enlarged frontal burr hole on the side with the most extensive injuries. The probe was placed over the lateral corticar surface of the frontal lobe.

As light enters the surface of the cerebral cortex, photons are scattered and Doppler shifted in a random fashion via moving blood cells and stationary tissue cells. A portion of the scattered photons mixes (heterodyne) on the surface of a photodetector and generates an electrical signal. The electrical signal from the photodetector contains frequency and power information. Frequency information is related to blood cell velocity, and the power information is related to blood volume. Blood flow is computed by determining the product of blood volume and blood velocity. The measurement of the blood flow by LDF is expressed here in arbitrary units (AU).

The signal was considered inadequate if the LDF signal was nonpulsatile or measured less than 5 AU. Typically, the reading on the LDF was nonpulsatile and less than 3 AU when placed over a hematoma or when the probe was turned upside down.

Monitoring of ICP, Arterial Blood Pressure, and Jugular Venous O2

The ICP and arterial blood pressure (ABP) were monitored with external pressure transducers and a multimoanular monitor (S & W, Albertslund, Denmark) using ventricular catheters and radial artery cannulas, respectively. Jugular venous O2 (SjO2) was monitored using optical catheters in the dominant jugular bulb (Oximetrix 3 System; Abbott Laboratories, North Chicago, IL), which was determined from the ICP response to jugular vein compression.14

Data Acquisition and Analysis

Data for LDF, ABP, ICP, and SjO2 were read into a computer using an analog-to-digital converter (DATAQ Instruments, Inc., Akron, OH). The data were sampled and stored at a rate of 16 samples per channel per second. Data were recorded continuously during the period of monitoring.

The essential steps in data analysis were: 1) division of data into multiple segments (epochs) of 15 minutes; 2) exclusion of epochs with artifacts on ICP and ABP waveforms; 3) exclusion of epochs with poor LDF signals; 4) exclusion of epochs with changes in CPP that were too large or small; 5) time averaging of the signals; and 6) linear regression analysis between LDF and CPP. The results were then presented graphically as autoregulation profiles.

After exclusion of the epochs containing artifacts, the data were averaged over six cardiac cycles using a waveform analysis package. The CPP was calculated from the difference between the mean ABP and ICP.

Epochs with LDF of less than 5 AU were excluded from further analysis, because according to our experience, LDF could give a reading of up to 3 AU when the probe was reversed. Epochs with CPP changes of less than 10 mm Hg were excluded to avoid the false conclusion that LDF has no relationship to CPP. These exclusion criteria were based on preliminary analysis of a number of epochs.

Epochs with abrupt changes in CPP (an increase of more than 0.1 mm Hg/second or a decrease of more than 0.4 mm Hg/second) were excluded from the analysis of autoregulation. This exclusion was based on results of animal experiments, in which the relationship between LDF and CPP was assessed in normal rats and spontaneously hypertensive rats. The LDF may change with changes in CPP, even within the normal range of CPP if the change in the latter is very rapid.1 It is believed that there is no time for the blood vessels to react if the changes are very rapid. We observed a similar phenomenon in the patients we monitored; an example is shown in Fig. 1.
The LDF and CPP data in each epoch were then subjected to linear and curvilinear regression tests using a commercially available statistical package (SPSS Inc., Chicago, IL). The linear regression correlation coefficient between LDF and CPP was used as an index of autoregulation. Positive or negative signs were attached to the index to indicate the direction of slope of the regression line. The index is an interval datum with limits between 1 and 2; a high value indicates poor autoregulation and a low absolute value indicates good autoregulation. The typical value for a patient with very low CPP was more than 0.8 and that for a patient with good outcome and adequate CPP was less than 0.2. For ease of presentation, an index of more than 0.5 is considered evidence of absence of autoregulation. An index between 2 and 0.5 is considered evidence of presence of autoregulation. An index of less than 2 indicates an unusual relationship between LDF and CPP; these conditions are considered separately in the Discussion section.

The maximum and minimum CPP values of all the segments for individual cases were plotted against time as a high–low line chart. The high–low lines were color (pattern)-coded to indicate the status of autoregulation against time. Hence, a profile of changes in CPP and autoregulatory status during the period of monitoring was then constructed for each patient. Patients were classified according to the pattern of the profiles. In the first group (intact autoregulation), all the segments examined had normal autoregulation. In the second group (transient impairment), some of the segments showed no autoregulation but subsequently recovered. In the third group (persistent loss of autoregulation), all the segments from a specific time onward showed no autoregulatory response.

Outcome Assessment and Analysis

The outcomes of the patients were assessed independently at 6 months by doctors in a rehabilitation center and classified according to the GOS. For statistical analysis, the outcome according to GOS was then reorganized into three categories: 1) satisfactory (good recovery and moderate disability); 2) severe disability; and 3) poor (vegetative state and death).

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The relationship between the pattern of autoregulatory response during intensive care unit monitoring and the categories of outcome at 6 months was then assessed on a $3 \times 2$-contingency table using the Mantel–Haenzsel test for linear association.

**Results**

A total of 31 patients underwent postoperative LDF monitoring (Table 1). In 28 of the cases LDF was started within 24 hours of head injury; in the remaining three, LDF and ICP monitoring were initiated after the patients’ condition deteriorated. The median duration of LDF monitoring was 3 days, with a range of 1 to 15 days. In five patients, although the intraoperative reading of LDF was satisfactory, the signal of LDF was persistently low, in the range of 0 to 1.5 AU during postoperative monitoring, and the LDF waveforms were absent. No useful data were obtained from these patients. Three of these patients had good recovery and two died. Hence, only data from 26 patients were analyzed. The failure to obtain useful data was mainly related to technical problems rather than to the patient’s clinical condition or outcome.

The number of useful 15-minute epochs for an individual case ranged from 14 to 104. A total of 879 epochs were analyzed. The relationship between LDF and CPP changed with time. Longitudinal analysis of all the epochs obtained in a patient revealed three patterns of progress. First, 11 patients who had persistent loss of autoregulation and progressive reduction in LDF had poor outcome: nine died and two were severely disabled. Second, five patients exhibited intact autoregulation during the stay in the intensive care unit; all of them had good outcome. Third, 10 of the 11 patients with transient loss of autoregulation had satisfactory outcome but the other had severe disability.

Three of the patients who died had no autoregulatory response from the beginning of monitoring. The other six patients who had died had variable periods, with intermingling epochs of autoregulation and epochs with no autoregulatory response, and eventually had persistent loss of autoregulation for a variable period before they died.

The LDF and autoregulation assessment had good correlation with clinical outcome at 6 months for head-injured patients. Persistent autoregulation impairment was associated with poor outcome ($\chi^2 = 17.93, p = 0.00002$; Table 2). Transient impairment of autoregulation did not always indicate poor outcome, provided that the impaired autoregulation responded to treatment. Five patients had transient impairment of autoregulation and experienced good outcomes.

**Examples of Profiles of Autoregulation**

The autoregulatory status as measured with LDF changed with time in most cases. Figure 2 (upper) represents a patient (Case 26) with head and chest injuries. The admission GCS score was 12. Multiple epochs of impaired autoregulation were found during the initial 3 days despite active treatment to maintain an adequate CPP and oxygenation. As brain swelling increased and adult respiratory distress syndrome set in, autoregulation became increasingly impaired until the patient died. Impairment of autoregulation preceded the final reduction of CPP.

Figure 2 (lower) represents a patient (Case 12) with head injury. The admission GCS score was 8.
In a study of iodoantipyrine method. The LDF test does not produce absolute values for blood flow in the microcirculation. However, LDF was found to change linearly with local changes provided the range of CPP changes needed to produce a false conclusion of normal autoregulation. Also, LDF demonstrates very important advantages over the other methods of measuring the CBF, namely high temporal resolution, rapid response, and continuous output.

The relationship between LDF and CPP, but not ABP, was used to assess autoregulation. In animal studies conducted previously, induced arterial hypotension and induced intracranial hypertension were found to have similar effects on cerebrovascular resistance (defined as CPP/LDF). The spontaneous ICP waves and ABP changes provided the range of CPP changes needed to assess autoregulatory status.

**Exclusion Criteria**

Five cases were excluded because of absence of LDF signals resulting from poor transducer–cortex contact. With experience this technical problem may be reduced. However, some conditions, such as subdural hematoma or prominent subarachnoid space, may predispose to the poor contact. Each monitoring technique has its limitation; hence, we believe that LDF may be useful as a component of multimodality monitoring.

A major portion of the epochs excluded were related to artifacts caused by normal activities in an intensive care unit, such as turning of the patient, chest physiotherapy, tracheal suction, and cerebrospinal fluid drainage. The exclusions were based on the absence of normal waveforms in the monitored parameters. Apart from the artifacts, there were only three exclusion criteria for the epochs: low signal on LDF, abrupt change of CPP, and changes in CPP that were too small. Each of these exclusion criteria was defined precisely to avoid observer bias.

One concern about using dynamic data is the effect of rate of change in ABP on the autoregulatory response. Our exclusion criterion for epochs with rapid change in ABP (an increase of more than 0.1 mm Hg/second or a decrease of more than 0.4 mm Hg/second) was based on a published animal study. It was found in another animal study that there was a short delay (3–13 seconds) in change of LDF after a sudden change in ABP. In a study of human autoregulatory response using transcranial Doppler sonography, the delay was also found to be dependent on the PaCO₂ state. To assess the effect of the rate of ABP change on the autoregulatory response in head-injured patients, we studied the LDF response to an induced cyclical change in CPP in head-injured patients; the preliminary results showed that when the rate of change in CPP was less than 0.55 mm Hg/second, there was no significant phase shift in LDF response (unpublished data). Hence, the criterion that we used may be too stringent, but it is the best available evidence at this stage.

The exclusion of epochs with CPP changes of less than 10 mm Hg was based on preliminary analysis of a number of epochs. The inherent noise level of LDF (related to arterial pulse, respiratory cycles, and vasomotion) made it difficult to conclude confidently that there was no change in LDF when the CPP change was small, even in patients with impaired autoregulation. We observed that in patients with impaired autoregulation (as shown with larger changes in CPP), a CPP change of less than 10 mm Hg may produce a false conclusion of normal autoregulation.

**Discussion**

**Autoregulation Assessment Using LDF and CPP**

Changes in CBF detected by LDF compare well with changes in CPP, but not ABP. The ABP and ICP are measured in millimeters of mercury; SjO₂ in percent; and red cell volume (Vol.), red cell velocity (Vel.), and LDF in arbitrary units.

Initially, multiple epochs of impaired autoregulation occurred. Raised ICP made it difficult to maintain an adequate CPP. After craniotomy for removal of contusion, CPP was maintained at a higher level, and autoregulatory responses were observed in all the subsequent epochs. This patient survived with moderate disability.

**Paradoxical Response in LDF**

There were epochs with paradoxical response in LDF, such as a fall in LDF while CPP rose, and vice versa. The overall incidence of these epochs with a negative relationship between LDF and CPP was 3%. These occurred more commonly in patients with high ICP, but they also occurred in patients with normal autoregulation profiles. Figure 3 shows an incidence of paradoxical response associated with plateau wave.

**Complications Associated With the Disk**

The contour disk could usually be pulled out after removing one skin stitch. The probe was caught on galeal stitches in two cases and more stitches had to be removed before it could be pulled out. There were no other complications related to the placement and removal of the LDF probe.
Rationale for the Index of Autoregulation

Near the breakpoints of autoregulation, the relationship between LDF and CPP is nonlinear. In head-injured patients, spontaneous CPP changes within a short period of time are seldom large enough to demonstrate the curvilinear relationship between LDF and CPP. At any one epoch we could only observe a small range of CPP. When there is an autoregulatory response, the changes in LDF over a period of time are independent of the change in CPP (Fig. 4). On the contrary, when autoregulation is impaired or the CPP is outside the range of autoregulation, LDF should change in the same direction as CPP.

We adopted a similar approach and used the linear correlation coefficient between the LDF and CPP as an index of autoregulation. When the index was close to 1, we were more confident that autoregulation was absent at the range of CPP during the epoch. Alternatively, when the index was close to 0, LDF was independent of CPP; hence, autoregulation was likely to be present.

Causes of Apparent Impairment of Autoregulation

Autoregulation may appear to be impaired if the CPP is above the upper breakpoint or lower than the lower breakpoint, or if there is a change in positions of the breakpoints. Our method of determining autoregulatory status cannot differentiate one situation from the others by assessing a single epoch. However, these can be differentiated by following the progress of autoregulatory status. Examining the autoregulation profiles of the patients with transient loss of autoregulatory response showed that there was usually a critical level of CPP below which no autoregulation was observed. This means that the autoregulatory response appeared to be impaired by low CPP or a raised lower breakpoint. Epochs with an impaired autoregulatory response that recovered after lowering the CPP were very uncommon and were observed on only three occasions. One example is a woman who experienced hypertension undergoing a craniotomy. The autoregulatory response using LDF was impaired when the mean ABP was 180 mm Hg. The autoregulatory responses became normal 1 hour later when the mean ABP dropped back to 120 mm Hg. Laser Doppler flowmetry can be a guide in the management of CPP.
Autoregulation was also found to be impaired when there was severe hypoxia (two patients) or very severe hyperventilation (PCO₂ of 2.1 kPa, one patient). Prompt treatment of the problem led to recovery of autoregulation.

Clinical Implications

Impairment of autoregulation may be caused by the primary brain damage or by secondary injuries. The deterioration in the autoregulatory response is a good indicator of the occurrence of secondary cerebral insults. Damage to the brain caused by the secondary insults can be prevented if the insults are reversed promptly. We demonstrated that some patients with transient impairment of autoregulation could have a good outcome.

Paradoxical Response on LDF

Paradoxical responses on LDF, that is falling LDF combined with rising CPP or vice versa, were observed in 3% of the epochs. Some of the epochs may be explained by a shift in the position of the probe when there was a dramatic change in brain swelling, such as a plateau wave (Fig. 3). However, it was also observed in some epochs that when CPP dropped to near the lower limit of autoregulation there was a rise in LDF and ICP. This may represent vasodilation in response to a drop in CPP in patients with relatively normal autoregulation. Because of the diversity of causes of this paradoxical response and its uncertain prognostic significance, it was excluded from the autoregulation profile.

Probe Design and Location

The probe that we used was a thin contour disk with a long optical fiber connecting to the monitor. The shape of the probe is suitable for insertion through a slightly enlarged burr hole. Once we inserted it in the subdural space, it wedged between the dura and the cerebral cortex, and because of the probe’s shape and the flexible cable, there was no trauma to the brain. There are many advantages in monitoring the pial cortical flow rather than that from a deep layer. If a probe penetrates the cortex, the LDF signal may drop by 60%. Moreover, the change in cortical blood flow in relation to the change in ABP is greater than the change of blood flow in the white matter.

Artifacts With LDF

The major problem was artifacts that occurred with movement of the patient or brain shift relative to the LDF probe. The probe may be fixed to the skull bone, but it cannot be fixed over the same point on the cortex. The value of the LDF changed with changes in hemoglobin and CO₂ levels. It may also change with strong external light, although we have not observed this when the probe is covered by scalp and skull. All these factors seldom changed rapidly and were considered to have an insignificant effect on autoregulation assessment over a short time. The LDF probe may lose contact with the cerebral cortex if the brain swelling subsides. The optical fiber may be broken or angled, in which case the LDF signal will be decreased and no pulsatility observed.

Future of CPP Management

The problem of spatial heterogeneity has been described. Artifacts could occur if the laser Doppler probe was located on a major cortical vessel. The use of fiber bundles to register LDF signals simultaneously from multiple locations may partly overcome the problem of spatial heterogeneity while maintaining a high temporal resolution. With advances in computer technology, all the filtering and analysis can be done on-line by computer. The regression coefficient can be used as the index for autoregulation. The changes in LDF may help us to determine the autoregulatory status that may guide us to a more rational and individualized management of CPP in head-injured patients.

Conclusions

The relationship between the change in CPP and LDF as an index of cerebral autoregulation was used in the study of 26 head-injured patients. The autoregulatory status changed with time as the patients’ conditions improved or deteriorated. The overall progress of the autoregulatory responses correlated with the outcome of the patients. The correlation between LDF and CPP has been demonstrated to be a useful index of autoregulation in monitoring head-injured patients.

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