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A laser Doppler system for monitoring of cerebral microcirculation: implementation and evaluation during neurosurgery

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Abstract

The aim of this study was to adapt and evaluate laser Doppler perfusion monitoring (LDPM) together with custom designed brain probes and software for continuous recording of cerebral microcirculation in patients undergoing neurosurgery. The LDPM system was used to record perfusion and backscattered light (TLI). These parameters were displayed together with the extracted heart rate (HR), pulsatility index (PI) and signal trends from adjustable time intervals. Technical evaluation was done on skin during thermal provocation. Clinical measurements were performed on ten patients undergoing brain tumour surgery. Data from 76 tissue sites were captured with a length varying between 10 s to 15 min. Statistical comparisons were done using Mann-Whitney tests. Grey and tumour tissue could be separated from white matter using the TLI-signal ($p < 0.05$). The perfusion was significantly higher in grey and tumour tissue compared to white matter ($p < 0.005$). LDPM was successfully used as an intraoperative tool for monitoring local blood flow and additional parameters linked to cerebral microcirculation (perfusion, TLI, heart rate and PI) during tumour resection. The systems stability opens up for studies in the postoperative care of patients with e.g. traumatic brain injury or subarachnoid haemorrhage.

Keywords: Microcirculation, Brain Tumor, Laser Doppler Perfusion Monitoring (LDPM), Pulsatility Index (PI), Neurosurgery

1. Introduction

Cerebral blood flow (CBF) is a parameter of utmost importance in neurosurgery and intensive care for patients with a wide range of disorders including traumatic brain injury [29], subarachnoid haemorrhage and brain tumour. Imaging techniques such as positron emission tomography [22] and Xe-CT [14] for assessment of CBF provide only “snap-shot” information that in addition would require transportation of unstable, critically ill patients. Reliable bedside monitoring of regional CBF are not yet available in daily routine however recently this problem is being addressed as a part of multimodal brain monitoring [3,2,1]. Continuous postoperative monitoring of local CBF in the damaged brain could improve early detection of secondary insults and reduction in blood flow while assessing the need for medical intervention. A measurement system for continuous assessment of CBF-parameters during surgery and postoperative care need to rely on robust and stable methods to be able to make its way into clinical routine.

During the last decade the interest for optical brain monitoring has increased. However, a majority of the scientific investigations and optical systems are still in the animal studies phase in neuroscience [13,39]. Few of the optical techniques have so far made their way into daily routine in the neurosurgical operating theatre and neurointensive care. Examples of emerging optical blood flow techniques are laser speckle contrast imaging [25] and indocyanine green dilution [20]. Other examples are the use of laser Doppler perfusion monitoring (LDPM) [36,38] and imaging (LDPI) [26,33]. An advantage of probe based point measurements compared to imaging systems is that the probe can be directly inserted into brain tissue and look ahead into obstructed areas without the removal of healthy tissue. LDPM has so far been used for intraoperative navigation and assessment of cerebral microcirculation during deep brain stimulation implantations (DBS). In this setting, a long stiff probe with optical fibre designed to fit the stereotactic frame system was used for LDPM recordings along pre-calculated trajectories [36,38]. These studies show that LDPM is capable of monitoring the dynamics of the cerebral microvascular blood flow. Already twenty years ago, LDPM was suggested as CBF-monitoring device together with intracranial pressure measurements [11]. Recently Dreier et al. applied LDPM on the surface of the brain using an optode strip combined with electrodes to study spreading ischemia 2009 [7] and epileptic activity 2012 [35] in patients with subarachnoid haemorrhage. LDPM is, however, still not an established monitoring method in the neurosurgical and neurointensive care setting. In the present study a LDPM system with custom made brain probes and software is presented and evaluated in two steps. The two step evaluation was done firstly by experimental evaluation on skin, and secondly by recordings of perfusion and total backscattered light in ten patients during tumour surgery.

Different approaches for a quick and easy overview of the dynamic processes in the acquired CBF-signals have been sought for [6]. The search for straightforward signal interpretations have resulted in various indexes where signal parameters are condensed to gain qualitative information [40]. From the perfusion signal it is easy to estimate heart rate (HR) as well as the so called pulsatility index (PI), commonly used for tracking blood flow changes which has been applied in transcranial Doppler and blood pressure measurements [5,4,10,31]. Furthermore the captured data need to be presented with a user friendly approach in order to optimize the feedback to the clinical interpreter. In this study we present an approach that support long-term recording of CBF-parameters by means of optics. The aim of the study was to introduce and evaluate LDPM together with custom designed probes and software for continuous recording of cerebral microcirculation in patients undergoing neurosurgery.

3. Methods

3.1 Laser Doppler system, brain probe and software

3.1.1 Laser Doppler perfusion monitoring

A LDPM device (Periflux 5000, Perimed AB, Sweden) was used in the system set up. It was connected to a personal computer with a data acquisition card (DAQ Card 6024E, National Instruments) and software (LabVIEW™ 2010, National Instruments Inc., USA). The custom made optical brain probes were used together with the LDPM device (Fig. 1a). Two signals are extracted from the system: the total backscattered light (TLI) and the perfusion (microvascular blood flow). The TLI signal is the summation of both AC and DC components from the photodetector and the perfusion signal represents the concentration of moving blood cells and their velocity. For details regarding signal processing see Nilsson et al. [24,23]. During intracerebral measurements, the TLI signal represents the diffuse reflection of light which is related to the tissue type whereas the perfusion is related to relative changes in the tissue's microcirculation. [36,38]. The total range of the perfusion and TLI signals are presented as 0 to 999 arbitrary units (a.u.) and 0 to 10.0 a.u. respectively. For all measurements, the DAQ sampling frequency (f_s) was set to 100Hz. The probe was tested in Motility Standard solution (Perimed AB, Sweden) before each measurement occasion in order to verify comparable perfusion and TLI levels between measurements. If necessary the system was recalibrated.

3.1.2 Brain probe

The probe was designed to fit the neurosurgical application with a flexible tip for easy fixation and smooth insertion to the area of study. Four optical fibres ($\varnothing_{\text{core}} = 125\mu\text{m}$, numerical aperture = 0.37) were aligned along the interior of the probe and fixated next to each other at the tip (Fig. 1c). This

corresponded to a fibre-fibre centre distance of 250 µm. The end of the probe tip was slightly rounded in order to avoid tissue trauma and could be fastened with sutures for stabilization during longer measurements. The probe's catheter-like design is similar to that of an external ventricular drain which enable continuous postoperative monitoring through a small burr hole in the skull and allows for probe extraction without reoperation. Two of the four optical fibres were connected to the LDPM device and the remaining two were available for complementary diffuse reflectance measurements. During the course of the project the probe design was revised and a second probe model was made, by changing the size of the exterior tip from $\varnothing = 2$ mm to $\varnothing = 1.7$ mm henceforth referred to as probe Model 1 and Model 2 respectively. The total length of the probe cable was approximately 5 m in order to keep the main equipment outside the sterile zone in the operating theatre. Prior to measurement the probe was sterilized using the STERRAD® protocol [15]. For further information regarding probe design see Rejmstad et al. [27].

3.1.3 Software

The software, developed in LabVIEW™ (National Instruments Inc., USA) made it possible to sample, store and display derived parameters and indexes of the captured LDPM signals as seen in Fig. 1b. The PI parameter [5,4,10] is calculated according to literature as in equation 1 where $Perf_{max}$ and $Perf_{min}$ corresponds to an average of the local (systolic) peaks and (diastolic) valleys in the perfusion signal respectively over the predefined time interval (10 s or more) while $Perf_{average}$ is the signal average over the same interval (see Fig. 4).

$$PI = \frac{Perf_{max} - Perf_{min}}{Perf_{average}} \quad (1)$$

Prior to the HR estimation the perfusion signal is low-pass filtered (cut-off frequency 20Hz) to remove high frequency noise and suppress detection at the dicrotic notch. The online heart rate estimator uses peak finding to sort out and count the number of heart beats per selected interval and convert that into HR. Features of the monitoring software contain presentation of the perfusion and the TLI signal, as well as the display of the HR and PI. In order to present trend curves, various time interval (e.g. 10, 20, 30 and 60s) can be set to calculate the average values for presentation. Figure 1b presents an example of the interface during a measurement.

3.2 Experimental evaluation of system and probe

The probe's function, were tested by measurements in Motility Standard. In order for the LDPM system to produce a perfusion signal with minimal noise, enough backscattered light from the tissue

(TLI > 0.5) was required. The system was thereafter calibrated for the selected type of probe. This procedure was performed before and after cleaning the probe and sterilization according to the STERRAD® protocol [15]. Secondly the probes were used for measurements of skin blood flow. The two probes (Model 1 and 2) were positioned on the face of the palm, about one mm apart, on one volunteering healthy person. Recordings were done before during and after a temperature provocation using an infrared heat source.

3.3 Evaluation during neurosurgery

3.3.1 Patients

Ten patients (6 female and 4 male, age 38 to 77 with an average of 59) referred for tumor surgery by the Department of Neurosurgery, Linköping University Hospital, were included in the clinical part of the study (Table 1). The patients were selected among individuals scheduled for craniotomy to enable measurement with direct contact to brain tissue. The selection was limited to surgical procedures where the research group has had previous experience with optical measurements. The clinical measurements were approved by the local ethics committee (M182-04, 2010/359-32) and written informed consent was received from the patient prior to each measurement.

3.3.2 Surgical measurement procedure

In order to evaluate the performances of the system and the brain probes in the clinical environment, measurements were done in relation to tumor resection and open skull biopsies. After opening of the skull the probe was manually inserted into a preselected brain tissue region while all other instruments and handheld devices were retracted to reduce the influence of movements that otherwise would affect the recorded signals. The probe was placed in three main types of tissue as defined by the surgeons' naked eye namely; white matter, grey matter and tumor. To receive stable signals the probe was kept at the same tissue site for at least 10 s up to several minutes, where the longest recording lasted for 15 min. In total 76 recordings were done at different tissue sites. Figure 2a presents an overview of the operation theatre and 2b a close-up of the probe fixation in the brain tissue.

3.3.3 Data analysis

Recorded signals were sorted into grey matter, white matter and tumor tissue. The sorting was based on the surgeon's visual inspection and all statistical tests were performed using this type of classification. The data was tested for normal distribution by performing a Ryan-Joiner test using Minitab statistical software (Minitab Inc., USA) on the LDPM signals perfusion and TLI. The result from the test indicated that the data was not normally distributed. As a result medians of perfusion and TLI were used for each group. Mann-Whitney tests were used to investigate the difference between

tissue groups. P-values < 0.05 were considered significant. Tumor type was defined by routine histopathological examination and the tumours were graded as high (grade III-IV) or low (grade I-II) according to the WHO classification of tumours [21].

4. Results

4.1 Experimental evaluation

Before the skin measurements the probes were placed in motility standard solution to compare the measured values between probes. The calibration of the system involves adjustment of the perfusion level using Motility Standard. Measurements with probe Model 1 gave a perfusion value of 238 ± 10 a.u. and TLI of 0.85 ± 0.02 a.u. while probe Model 2 had a perfusion value of 227 ± 11 a.u. and TLI of 0.66 ± 0.01 a.u.

Figure 3a presents the perfusion signal during a skin temperature provocation using probe Model 1 and probe Model 2. The probes were placed one mm apart on the face of the right arms palm on top of Abductor pollicis brevis. Figure 3b displays the corresponding perfusion trend curves using 10 s averages. Average perfusion, PI and HR for each 1 min period is presented below the trend curves. It is seen that the curves are following each other. The deviations in perfusion values are due to the tissue inhomogeneity [37].

4.2 Evaluation during neurosurgery

A summary of the tumor grade, used probe model and number of measurements sites for the patients is found in Table 1. One of the patients was excluded (Patient 7) from the study due to technical difficulties as one optical probe did not receive enough light for the LDPM system (TLI < 0.5) to produce a perfusion signal. In the remaining nine patients, recordings during surgery were fulfilled without technical failure and complications. At surgery one suspected brain tumor (Patient 2) was revealed as an abscess due to an infection and thus only measurements in white and grey matter were considered.

In Fig. 4 a-c an example of 20 s online recorded signals from grey matter, white matter and tumour tissue are displayed, originating from Patient 4. The mean values of perfusion, TLI, HR and PI over the 20 s recordings are presented in the notation-boxes. It is clearly seen that the TLI is higher in white matter compared to grey and that the reverse relation is found for the perfusion. In this specific case, the tumor presented an intermediate TLI with a clear pulsatile perfusion. The estimated HR from the perfusion signal corresponding well with the normal monitored heart rate in the operating theatre.

The scatterplot including the average perfusion from all 76 measurement sites between perfusion and TLI for white, grey and tumor tissue is presented in Fig. 5. Recordings were made from different tissue sites classified by the surgeon as to originate from tumor ($n = 28$), white matter ($n = 16$) or grey matter ($n = 22$). Ten values were excluded as they were not clearly classified into a tissue type by the surgeon's visual inspection. The authors suggest a TLI threshold of 1.7 a.u. in order to separate between white and grey matter in non-tumorous tissue sites in this patient group.

Figure 6 show box plots of the cerebral perfusion and total backscatter in the three tissue types as sorted by the surgeon's visual inspection. The median perfusion was highest in tumor tissue (109 a.u.) followed by grey matter (96 a.u.) while the lowest perfusion was found in white matter (42 a.u.). Significant difference in median perfusion was found between grey and white matter ($p < 0.005$, $n_1=22$, $n_2=16$). Likewise tumor and white tissue ($p < 0.001$, $n_1=28$, $n_2=16$) presented a significant difference in terms of perfusion. No significant difference in blood flow was found between grey and tumor tissue. The median TLI was highest in white matter (2.59 a.u.) with less than half as much in tumor tissue (1.13 a.u.) and approximately one third of that in grey matter (0.86 a.u.) respectively. The TLI values of the tissue groups showed significant difference ($p < 0.05$, $n_1=22$, $n_2=16$, $n_3=28$) between all groups.

The patient specific perfusion, TLI and PI are presented as a set of boxplots in Fig. 7 a-c. The results display the difference and data variability in perfusion, TLI and PI between patients. The PI showed a significant difference in medians between white matter and tumor tissue ($p < 0.05$, $n_1=16$, $n_2=28$) but no difference between the other groups using Mann-Whitney tests. There was a good agreement between the HR estimated from the perfusion signal and the patient monitoring system in the operating theatre ($r = 0.80$, $p < 0.01$, $n = 18$)

5. Discussion

This study shows that the optical measurement system, with custom made software and a specialised fibre optical probe, is capable of monitoring of cerebral microcirculation during brain surgery. Due to the difficulty in distinguishing between brain tissue types with the naked eye, a quantitative way of differentiation based on the TLI value was suggested. Analysis of the recorded data at sites where the surgeon gave a clear tissue classification resulted in a threshold between cerebral grey and white matter. In addition, a significant difference in TLI between tumour and white matter was found. This in combination with preoperative CT or MRI may help to improve the intraoperative navigation and localization of tumor tissue for areas embedded in white matter and obstructed from clear view. According to other studies using PET it has been found that malignant tumours with higher grades has higher blood flow compared to the normal surrounding tissue over tumours with a lower grade [34,8].

Using the LDPM technique as guide during surgical interventions has thereby potential to give the surgeon instant information about the tumour type.

The LDPM signals and the derived parameters (perfusion, TLI, HR and PI) has the potential to become a useful complement to existing intraoperative navigational techniques as well as for monitoring in postoperative care by providing information regarding local microcirculation in the sampled brain tissue volume. During this evaluation study the cerebral microvascular blood flow was found to be significantly higher in grey matter and tumor tissue compared to white matter. This is in accordance to previous studies where also grey and white matter could be separated by using the TLI [9,17,36,38]. It must thus be pointed out that the TLI-threshold set in this study, may vary between individuals and also due to probe configuration. In this case the latter assumption can be neglected as the same fibre type and distance between fibres were used for the two probe models. In order to establish a more general TLI-threshold further investigations could include recordings from a larger patient group. However, for a feasibility study of the LDPM system during neurosurgery using a flexible fibre optic probe the number of samples are considered sufficient.

It is well known that LDPM signals can be affected by movement artefacts. This is especially important to consider when using a handheld probe that will be influenced by the hand movements of the surgeon. This problem was dealt with by releasing the probe after proper placement at a selected tissue site. During longer measurement periods the probe could be sutured into place to further reduce movement influences of the signal resulting in a stable and reliable blood flow recording. The design of the optical probe is highly important when measuring regional microcirculation. Much effort and knowledge gained from previous work [19,27] has been put into use in order to make the probe small, flexible enough to suit the application. The advantage of Model 2 over Model 1 is the exterior probe dimensions which were slightly reduced while still flexible with a rounded tip. The fibre distances were kept the same resulting in similar sampling volumes. Previous studies based on Monte Carlo simulations using similar optical probe tip designs have estimated the optical sampling depth to approximately 1 mm in brain tissue [16,9,18]. The probe design could also be compared with previous investigations where a subdural optode-strip was used on the brain surface [7,35]. As the LDPM system can be equipped with multiple detectors our configuration also allows for multipoint recordings, but with the added advantage of measurement possibilities inside the tissue.

For future application the aim is to use the LDPM-system for long term monitoring of CBF in the neurointensive care, displaying both HR and PI together with the perfusion and TLI. The heart rate estimation extracted from the LDPM signal was compared to the existing patient monitoring system in the operating theatre and showed good agreement which indicates that the software works as intended. Pulsatility index, commonly used in ultrasound and transcranial Doppler equipment, is

proposed to reflect the level of vascular resistance in the circulatory system [32], however this is a question of debate in cerebral measurements. The PI-value will respond to drastic changes in the level of microvascular blood flow. This means that PI could be useful in detecting changes in the microcirculation during bedside monitoring which indicate a possible way of detecting reduced blood flow in the event of brain impairment. The software developed for neuromonitoring purposes used in this study could be used to quickly assess patient status when monitoring during longer periods. As changes over time often are relatively slow, trend curves can be built using averages over different time intervals e.g. from 10 to 60 seconds to keep track of and foresee dangerous levels of blood flow.

By combining the LDPM method with diffuse reflectance spectroscopy both blood flow and the oxygen saturation can be recorded as regional microcirculation parameters. This type of multimodal monitoring will give information about local oxygen delivery and utilization in the target area. Future work aim at measurements over longer periods (hours to a few days) in the neurointensive care unit where the probe is introduced during surgery for postoperative monitoring for example in the case of traumatic brain injury or subarachnoid haemorrhage. Additional combinations can involve pressure and microdialysis recordings. LDPM also has a potential to be used as a navigational supplement, due to tissue discrimination capabilities, in combination with other optical methods in neurosurgical applications, such as fluorescence guidance during brain tumor resection [12,30,28].

6. Conclusion

A LDPM system with custom designed probe and software has been adapted for measuring cerebral microcirculation. The system was evaluated on skin and intraoperative in brain tissue during neurosurgery. The study showed that the system could successfully be used as an intraoperative tool for monitoring local blood flow and several parameters linked to cerebral microcirculation (perfusion, TLI, HR and PI). Furthermore, the systems stability opens up for studies in the postoperative care of patients with e.g. traumatic brain injury or subarachnoid haemorrhage.

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The authors declare that they have no conflict of interest.

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Tables and Figures

Table 1 Patient diagnosis, probe model used for intraoperative measurement and number of recorded tissue sites for each patient

Patient	Tumor grade	Probe model	# Sites
1	Low	1	10
2	Non tumor	1	13
3		1	7
4	High	1	12
5	Low	1	5
6	High	1	5
7	Low	1	0
8	Low	1	10
9	High	2	10
10	High	2	4
	High

Fig. 1 a) Overview of the monitoring system, b)

Fig. 2 Evaluation on brain tissue during tumor resection a) operating theatre setup and b) probe positioned at the surgical site

Fig. 3 Evaluation on skin using probe 1 and 2, heat provocation (between min 1-2) showing the blood flow response a) perfusion signals and b) perfusion trends of 10 s averages divided by 1 min sections where the Perf, HR and PI are listed below

Fig. 4 LDPM signal with perfusion, TLI and derived parameters (notation box) from patient 4 in cerebral a) grey matter, b) white matter and c) tumor tissue, perfusion levels relevant to PI calculation are displayed using dashed horizontal lines

Fig. 5 Scatterplot showing LDPM data from measured tissue sites which are classified into grey, white or tumor tissue based on the surgeons visual inspection. The TLI threshold between grey and white matter is suggested to 1.7 a.u.

Fig. 6 Box plot with LDPM data showing medians of a) perfusion and b) TLI for the tissue types, grey matter (n=22), white matter (n=16) and tumor (n=28) displaying 25% and 75% quartiles, whiskers and outliers

Fig. 7 Boxplot of patient specific a) perfusion, b) TLI and c) PI displaying 25% and 75% quartiles, whiskers and outliers