Evaluation of the Pressure Measurement Function of an Implantable Multimodality Probe

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***Abstract*— To monitor changes in brain pathology, it is important to quantify multiple indices simultaneously. However, installing several probes at a measurement site enhances the risk of bleeding and infection. To solve this problem, a flexible multimodal, multichannel probe that can measure electrocorticographic signals, hemodynamics, and surficial temperatures of the cerebral cortex was previously developed. In this study, an intracranial pressure sensor was mounted on this probe to monitor increased intracranial pressure, which is a life-threatening condition caused by brain injury or other pathologies. As a result of animal experiments performed on two cats, the measurement accuracy and drift waveform were found to differ depending on the shape of the reinforcing plate. The result showed that plate A demonstrated a good correlation coefficient with the reference, while sufficient measurement accuracy was not achieved for the case of plate B. However, the correlation coefficient and limit of agreement were improved via filtering of the probe values. On the basis of these results, it can be considered that the probe captured changes in pressure, such as those due to respiration and pulse. However, its accuracy was reduced owing to the influences of the drift.**

I. INTRODUCTION

Observing multiple indices simultaneously is important to monitor changes in brain pathology in detail. However, most clinically used probes are designed to measure one parameter. Consequently, to measure multiple indices at the same time, it is necessary to install multiple probes at the measurement site despite the increased risk of bleeding and infection [1]. However, to solve this problem, in a previous study, flexible multimodal multichannel probes for simultaneous measurements of near-infrared spectroscopy (NIRS), electrocorticographic (ECoG) signals, and cerebrum surface temperatures were developed. With this probe, pathological neural activity was observed in a subject during surgery and during two weeks of post-operative monitoring [2]. On the other hand, increased intracranial pressure (ICP) is a serious and life-threatening condition caused by brain injury or other brain pathologies. When the ICP rises above a certain level, cerebral perfusion pressure decreases and causes an increase in the partial pressure of carbon dioxide in arterial blood and cerebral ischemia. This results in a further increase in the ICP. In this way, the ICP continues to increase. Further increase in the ICP causes cerebral herniation when the compressed brain parenchyma protrudes into the adjacent cavity. In the worst case, cerebral herniation results in brain death or severe paralysis. Hence, in this study, an ICP sensor was added to this probe, and the accuracy of ICP measurements was confirmed by animal experiments using two cats.

II. MATERIALS AND METHODS

A. *Probe Fabrication*

The developed probe was designed to measure ICP, ECoG, hemodynamics, and cortical temperature simultaneously. The parameters other than ICP were measured at multiple locations. In addition, by adopting flexible printed circuit technology, the probe had a thickness that was suitable for subdural implantations for mass production.

The probe head had an outer shape that was similar to that of the strip electrode commonly used in neurosurgery. For ICP measurements, a pressure sensor (Nova SensorP562, Amphenol Advanced Sensors, Pennsylvania, America) was mounted on the root of the substrate strip. For ECoG recordings, five platinum electrodes (diameters of 3 mm) were arranged at 1 cm intervals. To monitor hemodynamics, NIRS was used. Hence, the device included infrared light-emitting diode (LED) bare chips that emit at two different wavelengths (C770-40P at 770 nm and C810-40P at 810 nm, 0.4×0.4×0.25 mm, Epitex, Kyoto, Japan) and a photodiode (PD) bare chip that received the emitted near-infrared rays (PD2501, 1.3×3.1×0.3 mm, Epitex). The LEDs and PD were located on both sides of a platinum electrode to measure the same cortical area as the ECoG electrode. To measure cerebral cortex surface temperature, negative-temperature-coefficient thermistors were used (ERTJZEG103FA, 10 kΩ at 25 °C, 0.6×0.3×0.3 mm, Panasonic, Osaka, Japan). The thermistors were placed next to the ECoG electrode (Figure 1). After the assembly of the circuit, all electronic components were sealed with non-toxic, transparent silicone. Subsequently, all components and substrate were coated with a Parylene-C layer (thickness of 10 μm) to improve insulation and biocompatibility during chronic implantation. In this way, acute toxicity of the developed probe was removed from the probe surface that was exposed to the cortical surface. After these procedures, the total (maximum) thickness of the probe head became approximately equal to 0.7 mm.

B. *Reinforcing Plate against Distortion*

The pressure sensor detected pressure changes based on the piezoresistive effect. Conversely, a prototype probe was designed such that the probe head could bend along the brain

Figure 1. Proposed flexible multimodal, multichannel probe.

surface to have a flexibility that is suitable for subdural placements. Hence, there was a possibility that the pressure may be erroneously detected owing to the bending of the probe head. To eliminate this possibility, two types of reinforcing plates that prevent distortions of the probe head around the pressure sensor, namely, plates A and B, were suggested (Figure 2). Plate A is a metal plate with a width of 1 mm that fixes the outer circumference of the pressure sensor. Plate B is a metal plate that surrounding the pressure sensor, and its width along the edge of the probe head was designed to be 2 mm to make it less susceptible to distortion from the side of the probe head.

C. Probe Head for Cat Implantation

For implantations in the cat skull, the developed probe was cut. This left only the pressure sensor because the subdural parts of the cat's brain did not provide adequate space to embed the entire probe head. In addition, the side of the probe head was cut to minimize the gap between the skull and dura that was generated by inserting the probe head into the rounded skull (Figure 3).

D. Experimental Procedure

An animal experiment was conducted using two cats (cat 1 and cat 2) to verify whether the pressure sensor equipped with the reinforcing plate could measure minute pressure changes in a living body. The experiment was performed after the calibration of the probe with a water column. The experimental procedure was conducted at the place and using the method approved by the Animal Experiments Ethics Committee of Yamaguchi University.

1) Cat Surgery for Sensor Implantation

The cat was temporally anesthetized with sevoflurane in an anesthetic box, followed by immobilized with an intramuscular injection of ketamine and atropine. In the supine position, the trachea of the cat was incised and intubated to control breathing and to maintain sevoflurane anesthesia under a ventilator. In addition, the end-tidal CO2 was measured from the capnometer. A femoral artery and vein were subsequently cannulated to measure the arterial blood pressure and to infuse the lactate Ringer's solution. The cat was changed to the prone position, and then the head was fixed with a stereotactic device, After the skin incision, we made two burr holes in the left-occipital and right-parietal area to implant three types of ICP sensors.

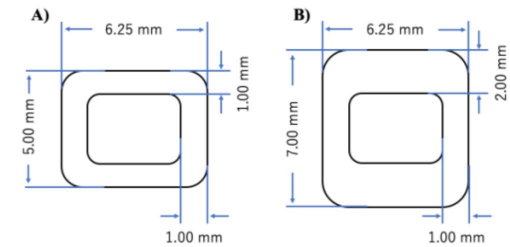

Figure 2. (A) Plate A and (B) plate B.

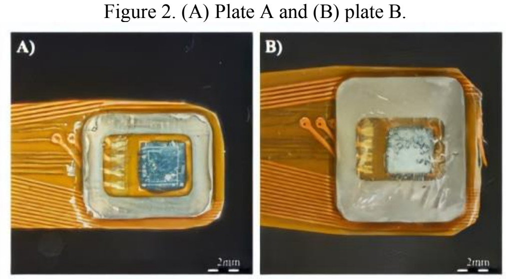

Figure 3. (A) Probe head with plate A and (B) probe head with plate B.

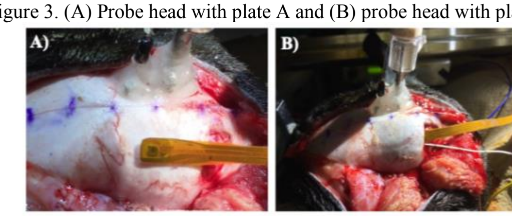

Figure 4. Locations of (A) the developed probe and (B) all sensors used in the experiment.

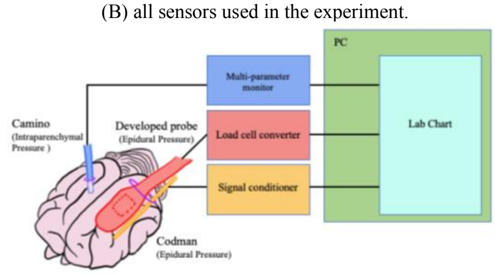

Figure 5. Setup for intracranial pressure (ICP) measurements.

2) Measuring the ICP

For reference, a puncture hole was made in the right parietal occipital region with a drill. Subsequently, the dura was incised, and a Camino sensor (110-4BT) was inserted into the brain parenchyma. For the implantation of the probe, the skull above the left occipital region was opened, and the developed probe was inserted between the skull and dura from the craniotomy site toward the coronal suture (Figure 4).

Table 1. Correlation coefficients between the prototype probe and reference sensor

		Epoch1	Epoch2	Epoch3	Epoch4	Epoch5	Epoch6
Cat 1 (plate B)	Without high-pass filter	0.59	0.72	0.88	0.63	0.69	0.52
	With high-pass filter	0.97	0.94	0.96	0.94	0.96	0.94
Cat 2 (Plate A)	Without high-pass filter	0.98	0.66	0.95	0.93	0.99	0.90
	With high-pass filter	0.99	0.97	0.99	0.99	0.99	0.98

Table 2. Limit of agreement of the prototype probe and reference sensor

		Epoch1	Epoch2	Epoch3	Epoch4	Epoch5	Epoch6
Cat 1 (plate B)	Without high-pass filter	-0.7 ± 1.0	0.4 ± 0.8	-0.2 ± 0.6	1.0 ± 0.9	-0.4 ± 0.9	0.7 ± 1.0
	With high-pass filter	0.0 ± 0.2	0.0 ± 0.3	0.0 ± 0.2	0.0 ± 0.3	0.0 ± 0.2	0.0 ± 0.3
Cat 2 (Plate A)	Without high-pass filter	0.3 ± 0.2	0.6 ± 0.8	0.3 ± 0.4	0.3 ± 0.5	-0.1 ± 0.6	0.5 ± 0.7
	With high-pass filter	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.1	0.0 ± 0.2	0.0 ± 0.1	0.0 ± 0.2

The probe with plate B was used in the experiment with cat 1, and the probe with plate A was used in the experiment with cat 2. In this procedure, only the developed probe was inserted in the experiment using cat 1, whereas the developed probe and a Codman sensor (21500BZY00397000) were inserted in the experiment with cat 2. However, the measurements obtained with the Codman sensor were not used in this study.

The camino sensor was connected to a multiparameter monitor (MPM-1), the prototype probe was connected to a load cell converter (M3LLC-S3-R4/A), and the Codman sensor was connected to a signal conditioner (PCU-2000). Transferred signals were recorded by the lab chart at a sampling frequency of 1 kHz. While measuring, the ICP was artificially changed by repeating the head-down state and horizontal state alternately three times. The head-down state was achieved by tilting the trunk of the cat by 20° for 5 min. The horizontal state was achieved by keeping the trunk horizontal for 5 min. States were referred to as Epoch1 to Epoch6 in the order in which they were observed (Figure 6).

E. ICP Processing

To compare the measurement accuracy of the prototype probe with that of the reference sensor, the correlation coefficient, limit of agreement (LoA), and the difference between the values of the probe and those of the reference sensor were calculated after alignment of the waveform times, calibration of values, and removal of noise.

Cross-correlation was employed for aligning the waveform times. The value of the probe was calibrated on the basis of the reference sensor value, and a moving average was then applied for noise removal. Following this, correlation coefficients were obtained by using values of the probe and those of the reference sensor. In addition, to evaluate the agreement between the probe and the reference sensor, the LoA was obtained by using a Bland–Altman plot [3]. The correlation coefficient and LoA were calculated for each Epoch because the correlation coefficient varied depending on the Epoch.

Drift indicates the fluctuation of the probe's baseline. To achieve long-term measurement, it is important to suppress drift changes given that microtransducers cannot be generally re-zeroed after insertion. To confirm the effects of drift, the correlation coefficients and LoA obtained on the basis of the filtered probe values and those obtained on the basis of the

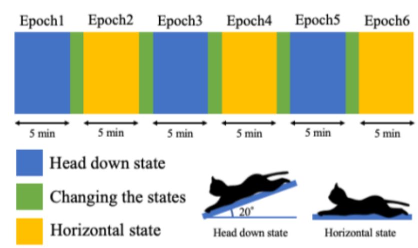

Figure 6. Changes in the states during ICP measurements.

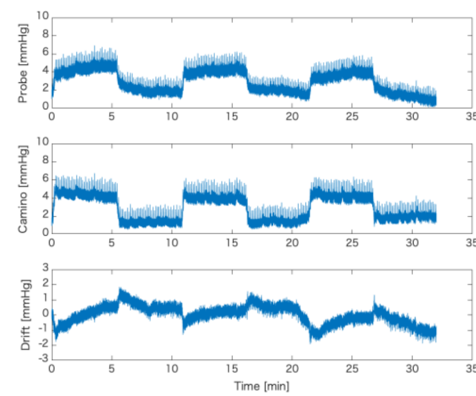

Figure 7. Pressure changes of the calibrated probe values, reference sensor values, and calculated drift in the experiment using Cat 1 and plate B.

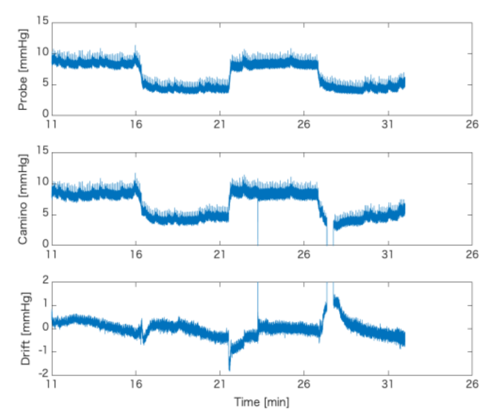

Figure 8. Pressure changes of the calibrated probe values, reference sensor values, and calculated drift in the experiment using Cat 2 and plate A.

unfiltered probe values were compared. The high-pass filter was used to reduce the effect of drift. The ICP was observed to fluctuate under the influence of breathing and blood pressure. Hence, the frequency of the filter was determined from the respiratory rate and pulse rate, which were recorded during the experiment.

Finally, to see the changes in drift throughout the experiment, the differences between the probe value and the reference sensor value were calculated by subtracting the reference sensor values from the calibrated probe values.

III. Experimental Results

The output of the prototype probe implanted in the skull shifted significantly in the negative direction compared to those before implantation. In addition, the changes in the output value of the probe became small during implantation. Therefore, calibration was applied after the experiments.

The correlation coefficients between the prototype probe values and reference sensor values are listed in Table 1. When the filter was not used, the correlation coefficient was 0.52 in the worst scenario for Cat 1. On the other hand, for Cat 2, the correlation coefficient was higher than 0.9 in all the Epochs. However, these values were improved via application of a high-pass filter even for Cat 1. The LoA of the developed probe and reference sensor are listed in Table 2. In the experiment involving Cat 1, the LoA was 1.0 ± 0.9 in the worst scenario without use of the filter; in Cat 2, the LoA was 0.6 ± 0.8 in the worst scenario. Similar to the correlation coefficient, the bias and the range of LoA were improved by using the high-pass filter.

The differences between the prototype probe values and reference sensor values ranged between approximately -2 mmHg and 2 mmHg (Figures 7 and 8). In the experiment that used cat 1, the drift increased in the head-down state and decreased in the horizontal state. Conversely, in the experiment with cat 2, the drift increased and then decreased each time the state changed, regardless of the state. Regarding the experiment of cat 2, the value before the first 11 min were excluded because the slope of the regression line of the scatter plot was different in this period compared with the values after this timepoint. This slope change was attributed to the effects of the use of water to the measurement site before the experiments.

IV. Discussion

Regarding the cause for the shift in probe output in the negative direction during implantation, it is possible that the reinforcing plates could not sufficiently eliminate the strain generated in the probe head via insertion of the probe into the skull.

From the results of the correlation coefficient and LoA analysis (Table 1 and 2), it was found that the measurement accuracy varied depending on the type of the probe (plate A or plate B). In addition, it could be seen that plate A achieved a high measurement accuracy. However, the importance and significance of these results cannot be addressed because the number of subjects is not sufficient.

The correlation coefficient and LoA were improved by eliminating the effect of the drift using the high-pass filter. From this result, it could be considered that the probe accurately captured changes in pressure, such as those due to respiration and pulse, and its accuracy decreased due to the influences of the drift.

The drift waveforms were different in the two experiments (Figures 7 and 8). This difference may be owing to the differences between the reinforcing plates. In addition, it could be considered that this difference affected the measurement accuracy. However, it is not clear how the shape of the reinforcing plates affected drift in this experiment.

V. Conclusions

In this study, a flexible, multimodal, multichannel probe that could measure ECoG, hemodynamics, cerebral cortex surficial temperature and ICP simultaneously was developed and animal experiments were conducted on two cats to confirm the probe's ICP measurement accuracy. From the experiments, it was found that the measurement accuracy and drift waveform differed depending on the shape of the reinforcing plate. In addition, the correlation coefficient and LoA were improved via filtering of the probe values. On the basis of the generated results, it can be concluded that the probe captured changes in pressure, such as those due to respiration and pulse. However, its accuracy was reduced owing to the influences of the drift. As the shape of the reinforcing plate may affect the measurement accuracy and the drift waveform, it is necessary to determine the optimum shape of the reinforcing plate in the future.

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