Bioelectronic Medicine

Monitoring the Injured Brain

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Traumatic brain injury is a serious public health problem in the United States, accounting for nearly 1.7 million injuries and 52,000 deaths annually. The initial brain injury is made worse by secondary events which include, but are not limited to, ischemia, swelling, cell damage and brain functions abnormalities which, while posing therapeutic challenges, offer therapeutic opportunities. Unfortunately, in spite of significant efforts, no effective indisputable treatment which would effectively alleviate consequences of this often devastating event currently exists. Multimodality neuromonitoring could provide early warning of secondary brain injury and guide individualized therapy. However, it is rarely done due to the complexity of using multiple devices and the increased risk of complications. This article presents a novel multifunctional smart catheter to continuously and accurately monitor multiple physiological, metabolic and electrophysiological parameters that are vitally important in guiding the care of patients with traumatic brain injury. In addition to measuring various crucial parameters, the developed smart catheter allows for drainage of excess cerebrospinal fluid as a therapeutic strategy to reduce intracranial pressure. The studies which were performed under a rat permanent middle cerebral artery occlusion model indicate that the smart catheter, a single probe, can dynamically detect changes in cerebral glucose, lactate, oxygen, glutamate, temperature, local cerebral blood flow and intracranial pressure that correlated with spreading depression. These results demonstrate that the smart catheter is capable of simultaneous and continuous measurement of multiple brain variables, within the pathophysiology ranges observed in brain injury. The smart catheter has the potential to improve our understanding of brain pathophysiology and advance the field of neuromonitoring into a completely new era in which medical decisions will be based on comprehensive, real-time measures of brain chemistry and physiology during the critical period immediately following a brain injury.

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INTRODUCTION

Traumatic brain injury (TBI) is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (1). It is a major cause of death and disability in both civilian and military settings, with large direct and indirect costs to society. The mortality from severe TBI is approximately 30% with a substantial proportion of survivors being left with significant disability (2). The initial brain injury is made worse by secondary events which include, but are not limited to, ischemia, swelling, cell damage and brain functions abnormalities (3–5) which, while posing therapeutic challenges, offer therapeutic opportunities. Pharmacological neuroprotective agents have so far failed to demonstrate a statistically significant effect when given after TBI (6). Therefore, current patient management strategies are directed toward optimizing the physiological environment of the injured tissue to minimize secondary insults (7–8). Multimodality monitoring, that is currently only partly available with the use of multiple devices, could provide a comprehensive assessment of the injured brain and hence enable immediate detection and prevention of irreversible neurologic injury (9–11). Such individualized treatment, informed by multimodality monitoring, has the potential to improve patient outcomes after TBI.

The current approach for multimodality monitoring patients with any type of acute severe brain injury is based on the insertion of multiple probes into the brain parenchyma (12–15). However, it is rarely done due to the complexity of using multiple devices and the increased risk of complications. Hence, even the available monitors are not always used. Monitoring of the injured brain has advanced little in recent decades and is limited mainly to intracranial pressure (ICP) and, less frequently, brain tissue oxygenation. This leads to suboptimal care based mainly on computerized tomography (CT) scans and observation of neurologic status, both of which are intermittent and usually indicate complete

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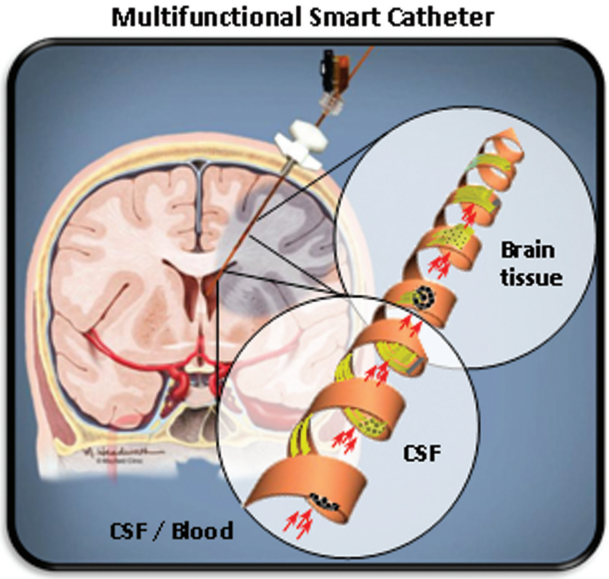

Figure 1. Conceptual drawing of a smart catheter for multimodality monitoring in traumatic brain injury: It can continuously and accurately monitor multiple physiological, metabolic and electrophysiological parameters in the injured brain. Microsensors outside the catheter monitor local brain tissue parameters and the ones outside monitor global cerebrospinal fluid (CSF) parameters. It can also work as a catheter to drain excess CSF.

damage. Part of the reason for this limitation is the lack of a simple, comprehensive and inexpensive monitoring device. Thus, there is a vital need for a single, accurate, multimodality device that can continuously monitor the key biochemical and physiological parameters in severely injured or ill patients and provide us with an "early warning system."

Recent progress in MicroElectroMechanical systems (MEMS) and nanotechnology permits the development of highly functional neural probes for diagnosis and treatment of brain diseases (16–18). The highly integrated probes can be made small and flexible, rendering their usage minimally invasive. The microsensors on the neural probe can achieve better spatial and temporal resolution with high sensitivity and selectivity, a feature highly desired in neuromonitoring applications. Hence, the adoption of MEMS technology has the potential to revolutionize brain multimodality monitoring by miniaturizing and integrating all the desired functions such as ICP monitor, brain oxygen tension monitor, cerebral microdialysis analyzer, and so on, into a single compact unit.

In this paper, we present a novel multifunctional smart catheter developed by multidisciplinary technologies to continuously and accurately monitor multiple physiological, metabolic and electrophysiological parameters that are critically important in guiding the care of patients with TBI (Figure 1). One of the unique aspects of the smart catheter is that it employs a novel packaging technique to assemble multiple microsensors on both the inside and outside of the flexible polymer tube while avoiding wiring and assembling problems associated with previous methods. In addition, the smart catheter allows for drainage of excess cerebrospinal fluid as a therapeutic strategy to reduce ICP. Therefore, this serves both as a monitoring and therapeutic device (19).

METHODS

Eight microsensors were first fabricated on the flexible polyimide (PI2611) substrate (Total thickness: 18 μm thick) based on MEMS and nanotechnology. A novel spiral rolling technique (20,21) was employed to form a flexible polymer tube without wiring and assembling problems associated with conventional approaches. The developed smart catheter exhibits an inner diameter of 0.7 mm, an outer diameter of 0.8 mm and a sensing length of 5 mm. Our technique allows the microsensors to be located either at inner or outer wall of the tube. The mechanical design and electrical operation of the microsensors were carefully chosen and tailored such that the potential electronic, thermal and chemical cross-talks among the microsensors were minimized. The nonideal cross-talks addressed during the course of sensor miniaturization and integration include electromagnetic interference (EMI); electrical feedthrough across conductive electrodes; chemical cross-talks among the electrochemical sensors; inductive coupling among the traces; finite traces resistance; and capacitive coupling.

To achieve the highest microsensor performances, several nano-/micro-fabrication techniques were developed for the smart catheter: 1) Silicon Nitride film (thickness: 80 nm) was directly sputtered on the PI2611 film to provide a better diffusion barrier against humidity (22), one of the major problems for flexible polymer MEMS devices; 2) Nanocrystalline polysilicon was developed by an aluminum-induced crystallization process to realize a highly sensitive pressure sensor on the flexible substrate (23); 3) Platinum nanoparticles were electroplated on the working electrode of the biosensors to achieve higher sensitivity by providing a large available surface and enhancing the electrocatalytic activity (24); 4) Iridium oxide nanoparticles were electroplated on the electroencephalography (EEG) electrodes to achieve a superior signal-to-noise ratio (SNR) and lower polarization rate (25); 5) Calcium peroxide and cerium oxide nanoparticles were integrated into the biosensor enzyme matrix to accurately measure the biochemical signals even under extreme hypoxia (26).

New structures and operating methods for the microsensors were developed to achieve high accuracy and reliability without cross-talk or interferences among the microsensors: 1) Temperature and cerebral blood flow microsensors were based on micromachined gold resistance temperature detectors (RTD) with a four-wire configuration (27). The temperature sensor operated with pulse excitation current without causing self-heating and its resistance measured by delta method cancelling the thermal electric effect (28); 2) The flow sensor employed a periodic heating and cooling technique with a constant-temperature mode to achieve the highest accuracy (29); 3) An oxygen electrochemical microsensor with three-electrode configuration was designed to achieve zero net oxygen consumption (24); 4) 3D ring-recessed microelectrodes were designed for the electrochemical biosensors to prevent both chemical and electrical cross-talks (30); 5) The temperature sensor was located outside the "thermal influence" area from flow sensor to prevent thermal cross-talk (29).

We have developed the multimodality monitor for the smart catheter. It is comprised of four units. First is the headstage, which performs signal amplification as well as provides mechanical interconnection between the smart catheter and the remote monitor. Second is the mixed signal front-end unit, which performs driving, signal conditioning and data acquisition. The processed outputs are then passed to the digital signal processing unit, which provides functions including data fusion, digital filtering, calibration, display control and recording. The final unit is the display, which contains all the visualization and provides human-machine interface. The multimodality monitor has the following features: 1) Display a total of 11 sensor channels including ICP, temperature, CBF, oxygen, glucose, lactate, glutamate and four full-band ECoG channels; 2) Perform on-demand data trend function; 3) Set the trigger level for the warning alarm as desired; 4) Transfer the recorded data easily to the USB flash drive; and 5) Reveal real-time interactions among user-selected sensor channels.

Table 1. Key features for the developed smart catheter microsensors.

Parameter	Working principle	Resolution	Accuracy	Range
Pressure	Polysilicon diaphragm based	0.1	1	0–50 mmHg
Temperature	Resistance temperature detector	0.03	0.1	25–45°C
Flow	Thermal diffusion – periodic heating	0.25	5	0–200 mL/100g-min
Oxygen	Electrochemical	0.2	1	0–160 mmHg
Glucose	Electrochemical	0.01	0.05	0.03–10 mmol/L
Lactate	Electrochemical	0.006	0.1	0.02–8 mmol/L
Glutamate	Electrochemical	0.1	1.5	3–150 μmol/L
ECoG	Depth electrode	0.01	0.02	0–200 mV

The *in vivo* application and performance of the smart catheter were tested in the permanent middle cerebral artery occlusion (MCAO) rat model. Experiments involving animals were approved by the Institutional Animal Care and Use Committee (IACUC) of the Feinstein Institute for Medical Research. Male Sprague Dawley rats weighing 250-300 gram (n = 6) were used as the subjects. Standard stereotaxic surgical techniques were used to unilaterally implant a precalibrated smart catheter into the neocortex using the following coordinates relative to bregma (AP: –1.5 mm, ML: 5.0 mm, DV: –5.0 mm). According to previous studies, the lateral location is equivalent to the penumbra of the ischemic area (31). Two small screws were inserted into the skull to anchor the dental cement for securing the smart catheter. Once the dental cement was dried, the skin was sutured and only the electrical connector of the smart catheter was left outside. The *in vivo* measurements were carried out one day after the smart catheter implantation. The MCAO surgery was performed according to the previous studies (32). A 4/0 nylon filament covered with poly-L-lysine was inserted through a puncture to the external carotid artery onto the common carotid artery. Multiple signals from the smart catheter were recorded once after MCA occlusion. Mean ± SD values were calculated for all the measured parameters.

RESULTS

Table 1 lists the important specifications for each of the developed microsensors on the smart catheter. The performances of the microsensors were compared with commercial devices *in vitro* for each of the different measures.

Spontaneous waves of depolarization appeared in the ischemic penumbra during the third hour after MCA occlusion. As shown in Figure 2, the first episode of spreading depression (SD) consisting of negative DC deflections followed by positive waves (3.8 ± 0.6 mV) appeared 210 ± 13 s after the occlusion. After a delay of 183 ± 11 s from the onset of the negative DC shift the smart catheter recorded increased brain glutamate (7.9 ± 3.1 μmol/L), decreased glucose (21 ± 11 μmol/L), decreased and oxygen (1.9 ± 1.2 mmHg), and increased lactate (24 ± 17 μmol/L). After that, intracranial pressure (1.1 ± 0.3 mmHg) was increased and brain temperature (0.21 ± 0.06°C) was increased.

CONCLUSION

Using a single device, we are able to record real-time changes in cerebral glucose, lactate, glutamate, oxygen, temperature, local cerebral blood flow and intracranial pressure. A system to correlate these variables to spreading depression has been established. These results demonstrate that the smart catheter can conduct the simultaneous and continuous measurement on multiple brain variables, within the ranges commonly observed in brain injury. Results further show the im-

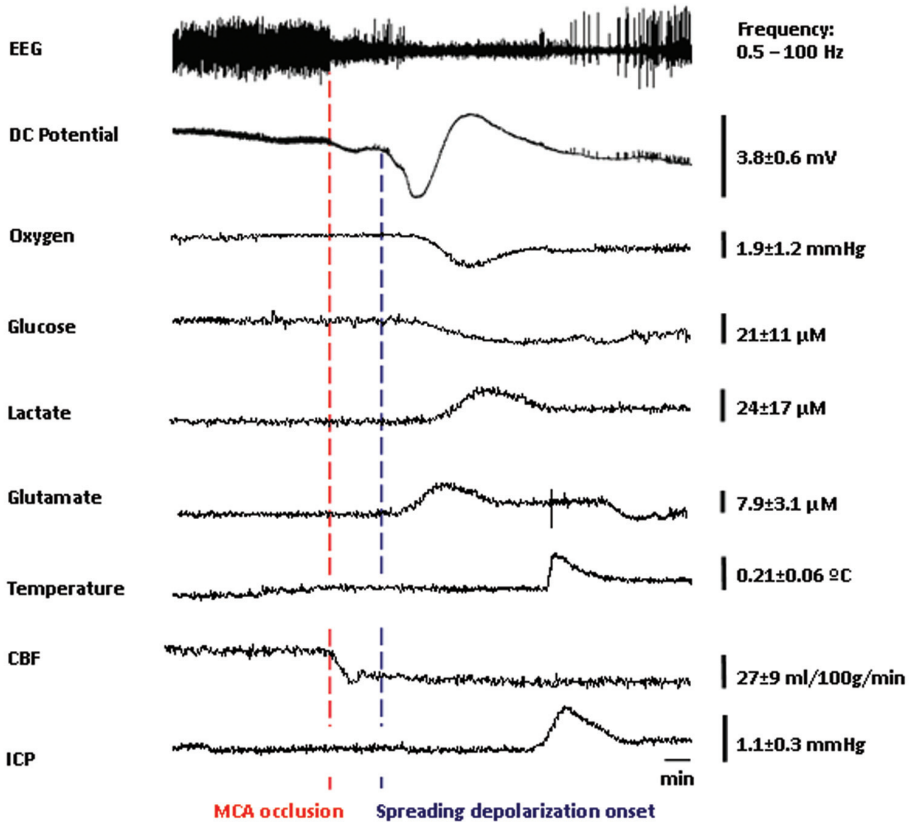

Figure 2. *In vivo* evaluation of smart catheter under permanent middle cerebral artery occlusion (MCAO) model: Experimental results after the first episode of spreading depression (SD) appeared after occlusion.

portance of multimodal measures of the same tissue to discover cause-effect relationships of candidate injury mechanisms. In that sense, the smart catheter represents a significant advancement in the field of neuromonitoring, opening up a completely new era in which medical decisions will be made based on extensive, real-time measures of brain chemistry and physiology during the critical period immediately following a brain injury, when the brain is most vulnerable to secondary insults. This advanced device not only can help with the clinical monitoring of brain-injured patients, but also serve a very valuable research device in the laboratory.

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DISCLOSURE

The authors declare that they have no competing interests as defined by *Bioelectronic Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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