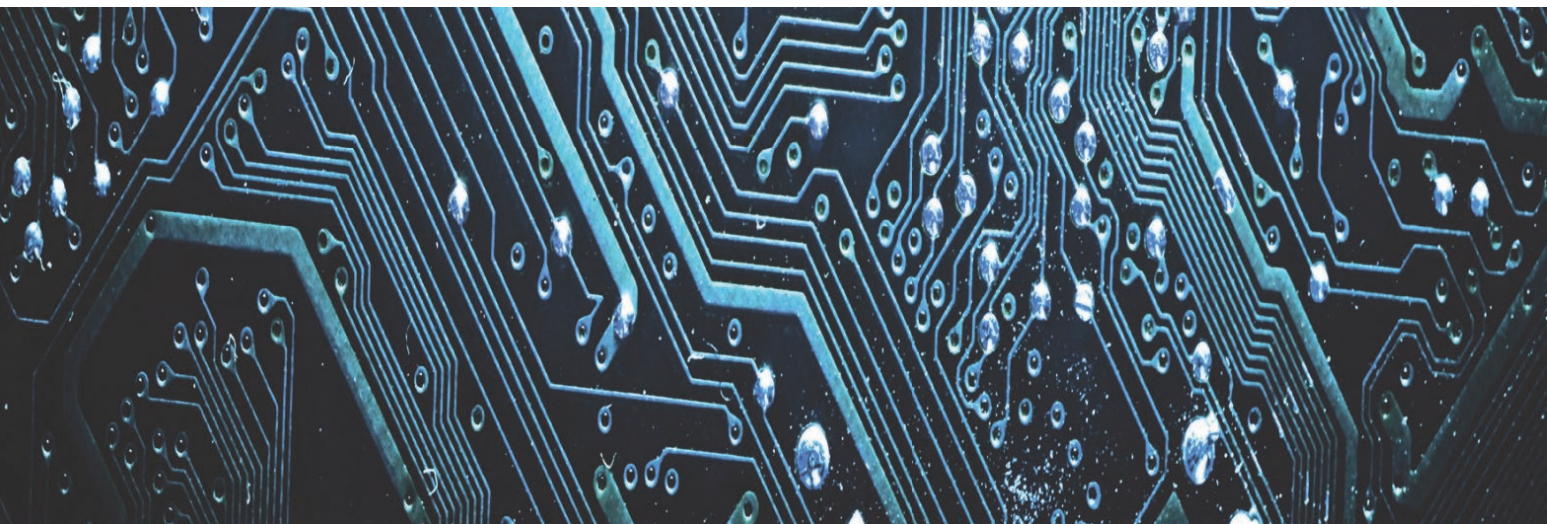


PERSPECTIVE OF USE OF KIWI IN BRAIN TRAUMA

Howard Brain Sciences Foundation



Perspective of Use of KIWI in Brain Trauma

ABOUT HBSF

HBSF (www.brainsciences.org) is a 501(c)(3) non-profit organization dedicated to achieving an all-encompassing understanding of human cognition and neurological disorders. Our research is focused on revolutionary, principle-driven solutions to cure intractable brain disorders. We are advocates for effective and meaningful brain research that is both interdisciplinary and thrives under a theoretical paradigm.

It is our belief that incorporating both the natural and social sciences in our research will bring us closer to unpacking and understanding how the human brain functions.

COVER IMAGE

The cover image was produced by Elena.

LEGAL DISCLAIMER

The mention of any individual, company, organization, or other entity in this report does not imply the violation of any law or international agreement, and should not be construed as such.

© HBSF 2019

ACKNOWLEDGEMENTS

The author would like to thank the team at HBSF who have gladly given their time and skills to assist in the editing, design, layout, and research. This report would not have been possible without their abundant contributions.

In Collaboration with ni2o

ni2o is a startup spun out of Oxford University. They are developing a brain computer interface (BCI) called the KIWI to treat diseases.

Perspective of Use of KIWI in Brain Trauma

EXECUTIVE SUMMARY

Brain is a complex network of several billions of interconnected neurons, distributed in a mixture of biological and biochemical constituent's compound; the whole works unceasingly in a perfect synchronization and equilibrium. Any injury to this dynamic system can cause severe, irreversible damages.

The frequency of traumatic brain injury (TBI) is currently higher than any other disease including breast cancer.¹ TBI occurs every 15 seconds in the US, generating 1.7 million new head injury victims per year, these events are responsible for 50,000 deaths, leave 80,000 individuals with permanent disabilities and cost more than 77 billion US \$ on average per year.¹ Therefore, TBI is a public health problem characterized by a combination of primary and secondary brain damages leading to the brain dysfunction. In fact, the underlying mechanisms are multifactorial complex, dynamic processes combining macroscopic and microscopic alterations which occur both in the acute, early sub-acute, late and chronic stages. Although a wide range of cellular and molecular mechanisms have been identified, the pathophysiology of TBI is not fully understood partly due to our insufficient knowledge on the brain physiology, biomechanics, and molecular features of this heterogeneous disease. The accurate diagnosis and clinical management of TBI is currently inadequate by the lack of accessible and precise correlation on how the various biological and molecular neural network dysfunctions connect or induce each other. Consequently, this complex and progressive brain injury, with very few effective approved treatment options, needs both short- and long-term therapeutic strategies to handle with the wide-ranging varieties of dynamic physio-pathological mechanisms involved.

Although basic science researches have greatly advanced our knowledge on brain functions and mechanisms, the accuracy of early accurate treatment and outcome-prediction remains poor even when all known prognostic factors are considered, suggesting that between the known basic patho-mechanisms several important unidentified links or unclear associations could have been performed by several non-monitored dynamic patho-mechanisms.

Perspective of Use of KIWI in Brain Trauma

BASIC SCIENCE KNOWLEDGE

1. Energetic Metabolism:

The brain represents only 2% of body weight but, at rest, its consumption of oxygen (O₂) is 5 mL / min / 100 g and that of glucose (Glu) is 31 μ mol / min / 100 g. These represent respectively 20% (O₂) and 25% (Glu) of the total consumption of the body. Cerebral blood flow (CBF), which is closely linked to the glucose consumption, represents 20% of cardiac output. This remarkable energy metabolism is clearly linked to the incessant cerebral intercellular activity. The understanding of the cerebral hemodynamic phenomenon accompanying cerebral aggression could be decoded through that of the physio and physiopathology of the energy metabolism.

2. Biomechanical Properties

In the rigid adult cranial box, the volume compensation capabilities are limited. Any increase in the contents, whatever its cause, could be accompanied by a reduction of CBF with intracellular ischemic edema. This cell edema will contribute to an additional increase in intracranial pressure (ICP) leading to the decrease in cerebral perfusion pressure (CPP) which is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). $CPP = MAP - ICP$.

On the other hand, occurrence of secondary cerebral insults, either due to systemic causes (hypotension, hypoxia, hypo- or hypercapnia, etc.) or to cerebral causes (seizure, vasodilatation self-regulation disturbances etc), precipitates ischemic evolution and ICP increases. It is well known that hypoxia and hypotension in cerebral aggression are major determinants of edematous processes.

3. The Volume Tolerance (VT)

VT of the cranial box can be estimated by a semi-logarithmic coordinate index, called pressure-volume index (PVI): $PVI = \Delta V / \text{Log} (P_p / P_0)$

Where ΔV is the volume added to the cerebro-spinal fluid (CSF), P_0 is the ICP at the basic state, and P_p is the ICP following the additional volume. This index is the theoretical volume required to raise ICP tenfold. The normal value of this index is approximately of 25 mL in young people.

This means, in principle, that the sudden addition of a volume of 25 mL increases the ICP value to that of MAP so that CPP becomes nil, and causes cerebral circulatory arrest.

Perspective of Use of KIWI in Brain Trauma

The low volume tolerance of the cranio-spinal box is governed by the Monroe-Kelly theory, which predicts that within this box, any increase in volume of any of the three components of the intracranial content (brain, CSF and blood volume) is counterbalanced by a reduction in similar global volume by the other two compartments. In practice the compensation mechanism is mainly due to CSF relocation and it is well known that the cerebral venous circulation, behaving like a Starling resistance, the cortical veins never collapse when the ICP rise and the gradient between cortical venous pressure and CSF pressure remains constant. This has two consequences:

The cerebral venous blood volume, which is probably the largest part of cerebral blood volume (4.2 mL / 100 g of tissue, approximately 50 mL for a 1300 g brain), remains approximately constant when intracranial hypertension (ICHT) develops.

The constancy of the gradient between cortical venous pressure and CSF allows CPP to be the same as the difference between MAP and ICP (which is by definition the CSF pressure) whereas from a physiological point of view the actual CPP is the difference between MAP and the cortical venous pressure.

In practice, it is the movement of CSF that buffers increases in brain tissue or cerebral blood volumes. This accelerated resorption of CSF will cause an exponential decrease of the ICP until its normalization. But the volume of transferred CSF is restricted. In adults, the ventricular system and subarachnoid spaces each contain 25 to 35 mL of CSF; the volume of 25 ml represents a critical volume since it practically corresponds to both the maximum volume of CSF that can be relocated out of the ventricular system and to the VT of the cranial box.

4. Intracranial Hemodynamic Properties

4.1 Brain self-regulations

Normal cerebral blood flow is approximately 50 mL / 100g / min. It is maintained relatively constant over a wide range of CPP variations (between 60 and 130 mmHg). Below and above these limits, the CBF varies proportionally with the CPP, although its molecular mechanisms are partly unknown. It should be noted that this principle of CBF stability during wide CPP changes is different from "physiological" autoregulation, which consists of increasing CBF during normal brain activation.

4.2 CO₂ reactivity

The variations of pressure of arterial CO₂ (PaCO₂) are accompanied by a variation in the same path of the CBF and it is well known that hypocapnia decreases the diameter of the cerebral vessels and that hypercapnia increases it. These caliber modifications are

Perspective of Use of KIWI in Brain Trauma

accompanied by a parallel modification of the CBF. A 5% increase in CBF per mmHg PaCO₂ can be used as the physiological average value of the CO₂ reactivity and the reactivity of the gray substance is greater than that of the white matter.^{2 3}

4.3 Reciprocal interactions capnia-autoregulation, CPP-reactivity to CO₂

PaCO₂ is an important modulator of CBF and cerebral autoregulation. Thus, hypercapnia vasodilatation limits the ability of additional vasodilation during a decrease in CPP. Conversely, at the upper limit of the self-regulating plateau, the vessels relaxed by hypercapnia increase their resistance less. The opposite phenomenon occurs during hypocapnia. In summary, hypercapnia shifts the upper and lower limits of the self-regulating plateau to the higher and lower CPP values, thus narrowing the self-regulatory plateau.

4.4 Biomechanical constraints and cerebral aggression

In brain pathology, the pressure volume index (PVI) characterizes the cranio-spinal volume–pressure relationship over the whole physiological range of ICP linked with the inter-relationships of the static and dynamic processes of formation, storage and absorption mechanisms of CSF. In addition it has been shown that the CSF contribution to ICP in severely head-injured patients accounts for only about 30% of the ICP rise while the majority of ICP is attributable to vascular mechanisms. Consequently, the PVI is a complex function of CPP, the trend of the CPP–PVI relationship being dependent on whether CPP is above or below the auto regulatory range for CBF, however the biomechanical constraints observed theoretically do not explain all the pathological phenomena observed in the clinical practice.

4.5 Physiology of energy metabolism and signal transduction in brain tissue

In human, the main excitatory neurotransmitter is an amino acid: glutamate. It is released by synaptic terminals and exerts its excitatory effects on postsynaptic neurons via specific ionotropic and metabotropic receptors. Extracellular glutamate concentrations are permanently finely regulated and its excitatory action is rapidly neutralized, mainly due to its reuptake by astrocytic processes that cover the synaptic cleft. This reuptake is essentially along an electrochemical gradient of Na⁺ in such a way that for each molecule of glutamate transported, three Na⁺ ions enter the astrocyte. This cotransport glutamate-Na⁺ is so narrow that the generated sodium flow reflects with great temporal precision the excitatory synaptic activity.

4.6 Coupling the glutamate cycle to the glucose cycle

It is well known that astrocyte glutamate reuptake is combined with Na⁺ entry. This entry of Na⁺ activates Na⁺ - K⁺ ATPase dependent pumps whose energy metabolism

Perspective of Use of KIWI in Brain Trauma

is glycolytic. The release of Na^+ exchanged with K^+ is therefore combined with an increased production of lactates. For its part, the astrocyte lactate generated by these processes regulating neurotransmission is used as an energetic substrate by the neurons after transformation into pyruvate and incorporation into the aerobic cycle of Krebs. From an energy point of view, the produce of anaerobic glycolysis is low and generates two molecules of ATP. One will be consumed during the activation of glutamine synthase, the second by that of the pump $\text{Na}^+ - \text{K}^+$ ATPase dependent. It may seem paradoxical that low energy efficiency glycolysis is preferentially used by astrocytes.

4.7 NO: a neurotransmitter and a vasodilator

NO is a molecular messenger produced by the oxidation of L arginine by an enzyme, NO synthase (NOS). There are several isoforms of the latter in the central nervous system. It appears that the controlled production, in small quantity, of NO by the constitutive NOS seems particularly adapted to a role of neurotransmission, whereas the permanent production of NO, in large quantity, by the inducible NOS correspond to a toxic function associated with the inflammatory processes. It is established that at the brain level the eNOS (Endothelial NOS) participates in cerebrovascular regulation.

4.8 Mechanisms linking cerebral activation to increased cerebral blood flow

The molecular mechanisms linking brain activation to increased cerebral blood flow have not been formally identified. Although it seems that astrocytes control the vasodilation through this mechanism: glutamate released by neurons in the synaptic cleft activates the astrocyte metabolico-receptors. A calcium wave caused by the activation of endoplasmic receptors IP_3 propagates to perivascular astrocytic prolongations where the calcium activation of a phosphor-lipase (not yet identified) causes the production of arachidonic acid (AA) from the stock of membrane phospholipids, the action of cyclooxygenase then leads to the production of prostanoid vasodilator derivatives. Thus, one of the neuron-astrocyte communications is at the center of the dynamic control of the blood vascular microcirculation.

4.9 Metabolism of free radicals

Compared to other organs, the brain is a producer of large amounts of free radicals during oxidative phosphorylation because of its high O_2 consumption related to its low mass. This production of free radicals physiologically happens at the level of complexes I and II of the mitochondrial respiratory chain and occurs during the transformation of arachidonic acid into prostanoids under the action of cyclooxygenase. Free radicals are mainly represented by superoxide anion ($\text{O}_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and hydroxyl ion (OH^\cdot). In general, free radicals are involved in the physiological processes of both necrotic and apoptotic cell death and the main line of defense against the permanent

Perspective of Use of KIWI in Brain Trauma

risk of oxidative stress, is due to glutathione (GSH) which is the main free radicals antagonist in the central nervous system. GSH is found in both astrocytes and neurons, although the latter contain smaller amounts. This synthesis is a form of metabolic cooperation between neurons and astrocytes. Glutamine from the glutamate-glutamine cycle between astrocytes and neurons is the best extracellular glutamate precursor for neuronal synthesis of GSH. If astrocytes are able to synthesize GSH from a large number of amino acids and peptides, the neuronal synthesis of GSH is dependent on the extracellular availability of cysteine. In practice, glycine and cysteine required for neuronal synthesis are provided by astrocytes that release significant amounts of GSH into the extracellular location. It is therefore not surprising that astrocytes have a powerful neuroprotective action against oxidative stress.

5. From Physiology to Pathology:

5.1 Glutamate toxicity and energy metabolism

Energy failure seems to be the essential element that moves from physiological excitation to pathological excitotoxicity which is caused by inhibition of astrocyte glutamate re-uptake. This point is fundamental in clinical not only in the start of anoxic or ischemic episodes where energy failure is the initial pathological event, but also in traumatic pathology where the causes of energy failure are more complex. They may be secondary to biochemical processes that, by themselves, contribute to energy failure during massive and sustained release of glutamate. Calcium activation of the constitutive NOS increases the production of NO and peroxynitrites that inhibit mitochondrial respiration. The increase in extracellular glutamate can cause the death of different brain cell populations by altering the transport of cystine etc. To these biochemical mechanisms are added the microcirculatory disorders of the "penumbra" area around a hematoma, a focus ischemia or an area of traumatic attrition. It is likely that the restriction of DSC increase during the massive release of glutamate may limit the glucose availability necessary for the rapid production of ATP required for astrocyte glutamate reuptake. This decoupling between DSC and glucose metabolism appears to be major event of the rupture of the metabolic homeostasis between neurons and astrocytes which leads to the energetic deficiency of the cerebral cell populations and to the extension of the initial lesions.

5.2 Physiopathology of the "penumbra"

A particular aspect of the pathophysiology of ischemic lesions is their propensity to extend from the ischemic center. Although less studied, it seems that the mechanism is the same in traumatic lesions and this, regardless of the overall reduction of DSC due for example to a major ICHT. In practice, the expansion of brain infarction appears to be related to the appearance of depolarization waves similar to "cortical spreading

Perspective of Use of KIWI in Brain Trauma

depression" (SD). SD is characterized by a propagated electrical activity wave of membrane's depolarization. The spread of SD is dependent of a glutamate process. These waves are accompanied by astrocytic calcium streams that could code for self-regulation of vasodilatation. Basically, an isolated wave of SD propagated in the zone of ischemic penumbra decreases tissue oxygenation at each of its passages. The reasons why DSC does not increase in the penumbræ are probably multiple and of varying importance depending on the nature of the pathology, ischemic or traumatic and each wave of depolarization increases the volume of the infarct.

MODERN APPROACH IN MECHANISMS INCRIMINATED IN TBI

It appears from the basic scientific data that cerebral energy metabolism and signal processing functions are closely related. At the molecular level the coupling of energy metabolism to signaling functions results in an intricate metabolism of glutamate and glucose. However, brain diseases including TBI are complexes dynamical progressing processes that initiate a multitude of macro and /or microscopic dissimilar pathological events which produce different time related clinical pictures within the same patient. In addition, there are growing body of evidence in support of an "individual-specific threshold" for TBI that varies based on individual intrinsic factors.⁴ Consequently, this multifaceted heterogeneity is considered as one of the most significant barriers to classify homogeneously this time depending myriad of patterns.

Therefore, for dynamic evolving lesions we need a predictable dynamical clustering multifactorial classification to find effective therapeutics solutions. However despite this heterogeneity we must not disregard the importance of our TBI's knowledge even though most of them represent only a disease's momentary snapshots. So according to brain life organization "brain injury is a puzzle, all the pieces are there but in the wrong order" and some dynamic patho-mechanisms appear and disappear with contradictory kinetics and/or fixed results. Nowadays, some of the limitations of these manual volume-pressure techniques are now being invalid and overcome as a result of innovative application using multimodality monitoring and applied computer technology which may prove to be a powerful aid in the investigation of TBI. So, the complex dynamic pathophysiology of neural injury is the primary barrier for developing a global sensitive and specific diagnostic tool from inert deduced data.

APPLIED COMPUTER TECHNOLOGY THAT KIWI COULD MONITOR.

The idea of a wireless micro-platform modality, could enable the monitoring of currently non-monitored dynamic mechanisms in the onset of any brain disease including primary

Perspective of Use of KIWI in Brain Trauma

and secondary microscopic brain injuries in TBI patients. The aim of neuro-monitoring is to recognize subtle changes in intracranial physiology as early as possible to initiate adequate knowledge, diagnostic, and therapeutic measures to prevent secondary brain damage. The complex and the speed of pathophysiology of neural injuries are major primary barrier for developing a global sensitive and specific understanding and diagnostic tools. So, the question is: may KIWI device allow, in neuro-critical care bedside, to monitor globally in a semi continuous and/or continuous manner systemic and/or cerebral insults in acute or chronic brain injury patients?

COULD KIWI BE AN “IN VIVO BRAIN NANO MULTI MODAL NEURAL PROBE”?

Either brain diseases or TBI activates a series of dynamic interlinked pathophysiological processes which initiate genetic factors in almost all the incriminated processes including oxidative stress, neuronal dysfunctions, neuro-inflammation, excitotoxicity, apoptotic cell death, neurodegeneration, reparative processes, synaptic plasticity, neurotransmitter alterations etc.^{5 6 7} Although great progress has been made with the aid of advanced technologies, such as advanced neuroimaging technologies Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS) Single-Photon Emission Computed Tomography (SPECT), Computed tomography scanner (CT scan) micro dialysis, and “omics” technologies etc., lacks in the dynamic temporo-spatial resolution of these patho-mechanisms, make it difficult to visualize the real specific dynamic mechanisms, locations and to isolate the affected pathways. They only traduce either different pathophysiological changes or the development of stable alterations that occurred in the cellular compartment or irreversible modification of pathways of (un)important, (un)identified or (un)clear associations caused by the several non-monitored (injuries occurring at the cellular and molecular levels can escape detection by conventional monitoring) dynamic patho-mechanisms which appear and/or disappear, over a certain time, after giving different intermediate or fixed alterations. Although, to date, only a limited number of brain parameters have been measured all together in vivo of awake animals or human. KIWI may answer this need of transitioning from static research screening to fast and dynamic systems biology tools to analyze simultaneous multimodal monitoring of brain activity, physiology, and neurochemistry which has become an important approach to explore and increase more specific and global understanding both in brain functions and pathology of brain diseases thus may open new opportunities to improve our understanding and discover new treatment modality of brain injuries.

CURRENT POSSIBILITIES OF KIWI DEVICE?

Perspective of Use of KIWI in Brain Trauma

Currently, some modern applied computer modalities are separately used in patients monitoring including:

1. ICP Monitoring

Intracranial pressure (ICP) is currently the predominant neurological-specific physiological parameter used to direct the care of severe TBI patients. Practice about indications and use of ICP monitoring in patients with TBI is well defined and standardized. Intra-parenchymal ICP monitors, on the other hand, are frequently used as a first-line monitoring method and are considered to be safe and of equal accuracy to intraventricular measurements.^{8 9 10} Devices have been developed offering the ability to monitor ICP and parenchymal temperature, CBF and other parameters directly or indirectly.

ICP is frequently used in TBI treatment to calculate the following indices of cerebrovascular reactivity:

The cerebral perfusion pressure (CPP) involving the patient's mean arterial pressure
PRx (correlation between ICP and mean arterial pressure (MAP),
PAx (correlation between pulse amplitude of ICP (AMP) and MAP),
RAC (correlation between AMP and cerebral perfusion pressure (CPP).

As also could be derived the compensatory-reserve-weighted intracranial pressure (wICP) which has recently been suggested as a supplementary measure of intracranial pressure (ICP) in adult traumatic brain injury¹¹ wICP (calculated as $wICP = (1 - RAP) \times ICP$; where RAP is the compensatory reserve index derived from the moving correlation between pulse amplitude of ICP and ICP).

ICP pulse-wave-patterns have been a research topic focusing on computerized analysis of morphological changes of ICP waves. Recently an algorithm has been introduced as Morphological Cluster and Analysis of Intracranial Pressure (MOCAIP) that might offer a promising way to measure cerebral perfusion and detect real-time cerebral hypo perfusion.¹²

2. Brain Oxygen Monitoring

Combined monitoring of ICP and brain tissue oxygen tension has shown to be superior to ICP alone.^{13 14} Several measuring devices have been developed to monitor the partial oxygen pressure with other items in the surrounding brain tissue.^{15 16 17} Cerebral oxygenation can be measured focally (brain tissue oxygen tension) or, more globally, by measuring the oxygen content in the cerebral venous outflow. Brain tissue oxygen

Perspective of Use of KIWI in Brain Trauma

tension indicates the balance between oxygen delivered to the tissue and its consumption in a specific area, and can indicate regional hypoxia if it falls below 15–20 mm Hg. Micro-sensor technology has recently been developed to allow continuous blood flow monitoring within the brain by use of thermal diffusion and laser Doppler probes.

3. Electrophysiological Monitoring. Continuous Electro-Corticography (ECoG)

It has been demonstrated that the development of multi-modal multi-channel probe for the simultaneous measurement of the near-infrared spectroscopy (NIRS), ECoG, and surficial temperature obtained from the cerebral cortex was carried out successfully with sufficient signal-to-noise (S/N) ratio and accuracy, to observe pathological neural activities.¹⁸

Spreading depolarizations (SDs) occur in 50-60% of patients after surgical treatment of severe traumatic brain injury (TBI) and are independently associated with unfavorable outcomes. SD were monitored by continuous electro-corticography (ECoG; median duration 79 h) following surgical treatment of severe TBI. In addition, it can reveal non-convulsive seizures that were not identified on simultaneous scalp EEG.¹⁹

4. Cerebral Micro-Dialysis (CMD)

Cerebral micro dialysis (CMD) is an invasive means of providing nearly continuous measurements of cerebral metabolism and local chemistry and is a promising tool that can detect signs of cellular distress before systemic manifestations of intracranial catastrophe show clinical manifestations. CMD allows bedside semi-continuous monitoring of patient brain extracellular fluid and can reveal unique information on brain chemistry before the brain ionic homeostasis becomes imbalanced and trigger molecular cascades with detrimental effects.²⁰ The most frequently studied molecules are glucose, lactate, pyruvate, glycerol and glutamate.²¹ However other molecules have been suggested for study such as: Serum albumin incriminated in blood brain barrier disruption,²² Serotransferrin for analyzing Free iron in the brain tissue,²³ Cystatin C incriminated in Increased autophagy,²⁴ Apolipoprotein A-1 and E playing a role in membrane remodeling due to cellular trauma²⁵, α -2-HS-glycoprotein (Fetuin-A) for Systemic response to cerebral injury²⁶ etc. So CMD is considered as a standard clinical monitoring modality as well as a research tool able to shed light on brain metabolism, inflammation, blood-brain barrier transit, therapeutic approaches, and drug effects on downstream targets.^{27 28}

5. Brain Multimodality Recording

Perspective of Use of KIWI in Brain Trauma

Optical fiber sensors have proven to be an attractive alternative to conventional measurement techniques. A multi-parameter brain sensor (MPBS) allows the simultaneous measurement of brain tissue oxygenation (ptiO₂), cerebral blood flow (CBF), intracranial pressure (ICP), and brain temperature with a single catheter.²⁹

On the other hand it has been demonstrated that the development of multi-modal multi-channel probe for the simultaneous measurement of the near-infrared spectroscopy (NIRS), ECoG, and surficial temperature obtained from the cerebral cortex was carried out successfully to observe pathological neural activities in subjects during surgery and post-operative monitoring, with no complications two weeks since the implantation, was confirmed.¹⁹

To the best of my knowledge, this will be the first time where multiple physiological, biochemical, and electrophysiological cerebral parameters will simultaneously be recorded from patients. I anticipate that the developed system will aid in gaining further insight into not only normal cerebral functioning but also pathophysiology of conditions such as epilepsy, stroke, and traumatic brain injury, neuro-degenerative diseases, brain tumor etc. In addition, these data coupled with omics results may give a new approach to brain physio and physiopathology with the help of computed system biology.

Perspective of Use of KIWI in Brain Trauma

ENDNOTES

- 1 M Faul, MM Wald, L Xu, VG Coronado Traumatic brain injury in the United States; Emergency department visits, hospitalizations, and deaths, 2002- 2006 [2010 stacks.cdc.gov].
- 2 Ainslie PN1, Duffin J. Integration of cerebrovascular CO₂ reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol Regul Integr Comp Physiol*. 2009 May;296(5):R1473-95. doi: 10.1152/ajpregu.91008.2008. Epub 2009 Feb 11.
- 3 Madden JA. The effect of carbon dioxide on cerebral arteries. *Pharmacol Ther*. 1993 Aug;59(2):229-50. Review.
- 4 Romeu-Mejia R, Giza CC, Goldman JT Concussion Pathophysiology and Injury Biomechanics. *Curr Rev Musculoskelet Med*. 2019 Feb 28. doi: 10.1007/s12178-019-09536-8. [Epub ahead of print]
- 5 Zhou Z, Austin GL, Young LEA, Johnson LA Mitochondrial Metabolism in Major Neurological Diseases. *Cells*. 2018 Nov 23;7(12). pii: E229. doi: 10.3390/cells7120229
- 6 Gowda R, Jaffa M, Badjatia N Thermoregulation in brain injury. *Handb Clin Neurol*. 2018;157:789-797. doi: 10.1016/B978-0-444-64074-1.00049-5.
- 7 Ko J, Hemphill M, Yang Z, Sewell E. Diagnosis of traumatic brain injury using miRNA signatures in nanomagnetically isolated brain-derived extracellular vesicles. *Lab Chip*. 2018 Dec 7;18(23):3617-3630. doi: 10.1039/c8lc00672e. Epub 2018 Oct 25.
- 8 Kirkman, M.A.; Smith, M. Intracranial pressure monitoring, cerebral perfusion pressure estimation, and ICP/ CPP-guided therapy: A standard of care or optional extra after brain injury? *Br. J. Anaesth*. 2014, 112, 35–46.
- 9 Kristiansson, H.; Nissborg, E.; Bartek, J.; Andresen, M.; Reinstrup, P.; Romner, B. Measuring elevated intracranial pressure through noninvasive methods: A review of the literature. *J. Neurosurg. Anesthesiol*. 2013, 25, 372–385.

- 10 Koskinen, L.-O.D.; Olivecrona, M. Clinical experience with the intraparenchymal intracranial pressure monitoring Codman MicroSensor system. *Neurosurgery* 2005, 56, 693–698.
- 11 Zeiler FA, Ercole A, Cabeleira M, Beqiri E. Compensatory-reserve-weighted intracranial pressure versus intracranial pressure for outcome association in adult traumatic brain injury: a CENTER-TBI validation study. *Acta Neurochir (Wien)*. 2019 May 3. doi: 10.1007/s00701-019-03915-3. [Epub ahead of print]
- 12 Hu, X.; Glenn, T.; Scalzo, F.; Bergsneider, M.; Sarkiss, C.; Martin, N.; Vespa, P. Intracranial pressure pulse morphological features improved detection of decreased cerebral blood flow. *Physiol. Meas.* 2010, 31, 679–695.
- 13 Keddie, S.; Rohman, L. Reviewing the reliability, effectiveness and applications of Licox in traumatic brain injury. *Nurs. Crit. Care* 2012, 17, 204–212. 185.
- 14 Le Roux, P.D.; Oddo, M. Parenchymal brain oxygen monitoring in the neurocritical care unit. *Neurosurg. Clin. N. Am.* 2013, 24, 427–439
- 15 Davies DJ1, Clancy M1, Dehghani H2, Lucas SJE3, Forcione M1, Yakoub KM1, Belli A1. Cerebral Oxygenation in Traumatic Brain Injury: Can a Non-Invasive Frequency Domain Near-Infrared Spectroscopy Device Detect Changes in Brain Tissue Oxygen Tension as Well as the Established Invasive Monitor? *J Neurotrauma*. 2019 Apr 1;36(7):1175-1183. doi: 10.1089/neu.2018.5667. Epub 2018 Oct 19.
- 16 Pinggera D, Petr O, Putzer G, Thomé C .Adjustable and Rigid Fixation of Brain Tissue Oxygenation Probe (Licox) in Neurosurgery: From Bench to Bedside. *World Neurosurg.* 2018 Sep;117:62-64. doi: 10.1016/j.wneu.2018.05.154. Epub 2018 May 30.
- 17 Limnusun K, Narayan RK, Chiluwal A, Bouton C, Ping Wang, Chunyan Li. Development of a brain monitoring system for multimodality investigation in awake rats. *Conf Proc IEEE Eng Med Biol Soc.* 2016 Aug;2016:4487-4490. doi: 10.1109/EMBC.2016.7591724.
- 18 Yamakawa T, Inoue T, Niwayama M, Oka F, Imoto H, Nomura S, Suzuki M Implantable Multi-Modality Probe for Subdural Simultaneous Measurement of Electrophysiology, Hemodynamics, and Temperature Distribution. *IEEE Trans Biomed Eng.* 2019 Feb 28. doi: 10.1109/TBME.2019.2902189. [Epub ahead of print].

- 19 Eriksen N, Pakkenberg B2, Rostrup E Neurostereologic Lesion Volumes and Spreading Depolarizations in Severe Traumatic Brain Injury Patients: A Pilot Study. *Neurocrit Care*. 2019 Apr 9. doi: 10.1007/s12028-019-00692-w. [Epub ahead of print].
- 20 Zhou T, Kalanuria A Cerebral Microdialysis in Neurocritical Care. *Curr Neurol Neurosci Rep*. 2018 Oct 23;18(12):101. doi: 10.1007/s11910-018-0915-6.
- 21 Hertle, D.N.; Santos, E.; Hagenston, A.M.; Jungk, C.; Haux, D.; Unterberg, A.W.; Sakowitz, O.W. Cerebral glucose metabolism and sedation in brain-injured patients: A microdialysis study. *J. Neurosurg. Anesthesiol*. 2014, doi:10.1097/ANA.0000000000000107.
- 22 Blyth, B.J.; Farhavar, A.; Gee, C.; Hawthorn, B.; He, H.; Nayak, A.; Stöcklein, V.; Bazarian, J.J. Validation of serum markers for blood-brain barrier disruption in traumatic brain injury. *J. Neurotrauma* 2009, 26, 1497–1507.
- 23 Park, U.J.; Lee, Y.A.; Won, S.M.; Lee, J.H.; Kang, S.-H.; Springer, J.E.; Lee, Y.B.; Gwag, B.J. Blood-derived iron mediates free radical production and neuronal death in the hippocampal CA1 area following transient forebrain ischemia in rat. *Acta Neuropathol. (Berl.)* 2011, 121, 459–473.
- 24 Liu, Y.; Cai, H.; Wang, Z.; Li, J.; Wang, K.; Yu, Z.; Chen, G. Induction of autophagy by cystatin C: A potential mechanism for prevention of cerebral vasospasm after experimental subarachnoid hemorrhage. *Eur. J. Med. Res*. 2013, 18, 21.
- 25 Mahley, R.W.; Huang, Y. Apolipoprotein e sets the stage: Response to injury triggers neuropathology. *Neuron* 2012, 76, 871–885.
- 26 Wang, H.; Sama, A.E. Anti-inflammatory role of Fetuin-A in injury and infection. *Curr. Mol. Med*. 2012, 12, 625–633.
- 27 Carteron L, Bouzat P, Oddo M. Cerebral Microdialysis Monitoring to Improve Individualized Neurointensive Care Therapy: An Update of Recent Clinical Data. *Front Neurol*. 2017 Nov 13;8:601. doi: 10.3389/fneur.2017.00601. eCollection 2017.
- 28 Carpenter KL, Young AM, Hutchinson PJ Advanced monitoring in traumatic brain injury: microdialysis. *Curr Opin Crit Care*. 2017 Apr;23(2):103-109. doi: 10.1097/MCC.0000000000000400.

29 Musolino ST, Schartner EP, Hutchinson MR, Salem A. Improved method for optical fiber temperature probe implantation in brains of free-moving rats. J Neurosci Methods. 2019 Feb 1;313:24-28. doi: 10.1016/j.jneumeth.2018.12.013. Epub 2018 Dec 19.