A Clinical Test for a Newly Developed Direct Brain Cooling System for the Injured Brain and Pattern of Cortical Brainwaves in Cooling, Non-cooling and Dead Brain

By

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ABBREVIATIONS

CPP - Cerebral perfusion pressure

CSF - Cerebro spinal fluid

CT scan - Computed tomography scan

DIVC - Disseminated intravascular coagulopathy

EVD - External ventricular drainage

GCS - Glasgow coma score

GOS - Glasgow outcome scale

hr - Hour

HUSM - Hospital Universiti Sains Malaysia

ICP - Intracranial pressure

ICU - Intensive care unit

ISS - Injury severity score

MAP - Mean arterial pressure

mls - Mililiters

PbtiO2 - Partial pressure of brain oxygen

PtiO2 - Brain oxygen

SD - Standard deviation

SPSS - Statistical Package for Social Sciences

TBI - Traumatic brain injury

Abstrak

Satu sistem penyejukan setempat kepada otak telah dihasilkan untuk tujuan penyejukan otak yang cedera dengan suhu yang tepat. Kebekesanan, keselamatan dan praktikaliti sistem ini telah dikaji secara klinikal di kalangan pesakit-pesakit kita. Pesakit yang dimasukkan dalam kajian kita dipecahkan dalam 2 kumpulan, iaitu penyejukan otak pada 32 °C dan kontrol. Kesemua pesakit menjalani operation otak iaitu ‘decompressive craniectomy’ dan dipantau melalui tekanan otak, oxygen setempat otak, suhu setempat otak dan juga gelombang otak. Pesakit yang menerima rawatan penyejukan otak setempat didapati mempunyai ‘extended Glasgow Outcome Scale’ yang lebih baik pada masa keluar hospital dan 6 bulan lepas rawatan. Keputusan yang menunjukan pesakit yang menjalani rawatan penyejukan otak mempunyai tekanan otak yang lebih rendah, suhu otak yang lebih normal dan gelombang otak yang lebih normal. Manuskrip ini juga menunjukkan gelombang otak pesakit yang meninggal dunia.

Abstract

A direct brain cooling system was newly innovated purposedly to ensure direct delivery of therapeutic hypothermia at a selected constant temperature to the injured brain. The practicality, effectiveness and safety of this system were tested clinically in our initial series of fourteen patients with severe head injuries. The patients were randomized into two groups – direct brain cooling at 32°C and the control group. The patients underwent standard decompressive craniectomy. Post operatively, all of them received intracranial pressure, focal brain oxygenation, brain temperature and direct cortical brainwave monitoring. The direct brain cooling group did better in the Extended Glasgow Outcome Scale at the time of discharge and at six months after trauma. This could be due to a trend in the monitored parameters; reduction in intracranial pressure, increment in cerebral perfusion pressure, optimal brainredox regulation, near-normal brain temperature and lessening of epileptic-like brainwave activities are likely reasons for better outcomes in the cooling group. Finally, this manuscript depicts interesting cortical brainwaves during a transition time of being alive to dead. The demonstrated cortical brainwaves are thought as obeying the principles in quantum physics.

Keywords: brain cooling, severe head injury, intracranial pressure, brain oxygenation, brain temperature, brainwaves, decompressive craniectomy, quantum brain

Introduction

Traumatic severe head injury is commonly associated with undesirable outcomes. This is likely due to complex pathophysiology underlying severely injured brain (Polderman 2004a; Jackson TC 2019; Nortje and Menon 2004). The proposed pathophysiological mechanisms underlying head injury revealed several important abnormalities, include; a) the activation of caspase enzymes, (b) presence of mitochondrial dysfunction, (c) increase in the local secretion of various vasoactive mediators secreted by the endothelium and excitatory neurotransmitters, such as glutamate and free oxygen radicals, (d) disorders of intracellular ion concentrations, (e) overexpression of the inflammatory and immunological responses, f) presence of epileptic activity, (g) disruption in blood-brain barrier and presence of vascular permeability with pathological edema as well as brain swelling, (h) abnormal microcirculatory brain circuits and presence of intra- and extra-cellular acidosis, and (i) expression of immediate early genes and cold shock proteins. Despite the vast understanding in its basic pathophysiology, clinicians were left with the removal of the surgical lesions, decompressive craniectomy and ICP management in treating this complex disease. However, in 2004 Poldermann and recently in 2019, Travis and Patrick have published a review article on this issue and highlighted the benefits of induced hypothermia on the injured brain (Polderman 2004a; Jackson TC 2019). They argued the true benefit of mild hypothermia lies in mitigating the aforementioned pathophysiological responses of brain injury. A combination of vast understanding in basic pathophysiology and the mounting evidence from animal studies have reproducibly shown mild hypothermia is profoundly neuroprotective has opened to several clinical trials for hypothermia in head injury (Ding et al. 2004; Luan et al. 2003; Oku T 2009). Unfortunately, despite numerous clinical trials made, the results were not convincing enough with level III of recommendation for optional and cautious use of hypothermia for adults with TBI (Ahmed, Bullock, and Dietrich 2016; Crompton et al. 2017; Lee et al. 2010; Peterson, Carson, and Carney 2008; Andrews et al. 2017; Clifton et al. 2001; Clifton et al. 2011). The discrepancy between the laboratory and clinical results could be due to the method of brain cooling and the mixture of different severity for the recruited patients in the studies.

In 2014, Z Idris et al. published a direct regional brain cooling study, which disclosed better outcomes in patients who had decompressive craniectomy and were treated with direct brain cooling irrigation at 30 to 36°C (Idris et al. 2014). The study was designed in such a way that the authors tried to minimize the confounding variables, which might influence the outcomes. With this background study, the authors had collaborated with a group of local engineers to expand the study and created a system (machine) that can set the irrigation fluid at certain selected values. The machine was created in such a way that the temperature of the fluid was kept constant throughout the irrigation period. Therefore, the purposes of this manuscript are: a) to present the technical part of this newly innovated brain-cooling system; b) to have a preliminary clinical study on the outcomes and safety of this system; c) to investigate the effect of direct brain cooling on the monitored intracranial pressure (ICP), cerebral perfusion pressure (CPP), focal brain oxygenation ($PtiO_2$), brain temperature and brainwaves; and finally d) to demonstrate a peculiar and interesting morphological feature of cortical human brainwaves transition from being alive to dead in one of our recruited patients. Since from our literature review, there was no such publication that correlates direct cortical brainwaves with such a transition, the finding is believed to be the first of such kind.

Materials and Methods

The general objective of the study is to determine the effects of direct focal brain cooling on severely injured brain. The specific objectives are 1) to investigate the effects of direct focal brain cooling on

intracranial pressure and cerebral perfusion pressure in severely injured
brain of GCS 4-7, 2) to investigate the effects of new innovations brought to focal brain cooling therapy machine on temperature regulation of cooled Hartman solutions, 3) to investigate the effects of direct focal brain cooling therapy on Glasgow outcome scale-extended (GOSE), 4) to investigate the effects of direct focal brain cooling on brainwave analysis.

The methodology is divided into two parts: A) A description on the newly innovated direct brain cooling system, and B) An initial clinical study using the system to investigate its feasibility, effectiveness and safety.

The inclusion criteria for the study are 1) patient with age 12 and above, 2) severe head injury with GCS score of 4-7, 3) no premorbid conditions prior to the accident, including history of seizures, 4) able to be followed up after 6 months being discharged from the hospital, 5) require neurosurgical intervention, either craniotomy or decompressive craniectomy, 6) consented by next of kin or guardians. Exclusion criteria are 1) patient with penetrating brain injury, 2) patient with significant drop in blood pressure (SBP <90/ DBP <60) and hypoxia prior to admission, 3) patient with fixed and dilated pupils bilaterally, 4) patient with severe injury to other organ systems which may lead to marked morbidity or even mortality, 5) patient with concomitant traumatic spinal cord injury, 6) patient known to suffer from immune or neurological diseases, 7) severe head injury with only extradural hematoma. Withdrawal criteria are 1) patient who has significant drop in blood pressure (SBP <90/ DBP <60) and hypoxia during the study, 2) patient who has cardiac arrest and requiring cardiopulmonary resuscitation

during the study, 3) patient who developed pupil fixed and dilated during the study, 4) family members who consented refused for study to be continued.

Part A

A newly innovated direct brain cooling therapy system was innovated by a local group of neurosurgeon and engineer. The aim of the therapy is to overcome the drawbacks of conventional technique in brain cooling. A conventional technique can be divided into two methods: external and internal brain cooling methods. The first method includes the use of cooling blankets, ice packs, alcohol baths, cold-water immersion, cold-saline gastric lavage, and local cooling using helmet devices. The second internal brain cooling method uses a central venous catheter to either infuse or directly administer cool saline to reduce the blood temperature by convection. However, these two methods have some disadvantages, such as complex implementation particularly in obese patients, high nursing requirements, intense skin vasoconstriction that caused shivering, slow onset of the desired temperature and erratic temperature maintenance for the first method, whilst systemic complications, namely pneumonia and cardiac instability was observed in the second method. Based on these arguments and with an advancement in the microelectronic technology, a brain coolant instrumentation system can be simplified by using System on Chip (SoC) and Microelectronic Mechanical System (MEMS) based sensor. Thus, in this project, simple instrumentation of brain coolant that can deliver focal cooling using Programmable System on Chip (Cypress PSoC 6 microcontroller CY8CKIT-062-BLE) from Cypress and MEMSbased temperature sensors were made. This instrument is a simple and direct delivery of cooling fluid into the localized injured brain area and precisely delivers a constant temperature of the infused fluid.

An adjustable temperature chamber where the sterile Hartmann's solution was placed is directly connected with a piping and ventricular catheter system that goes to the injured brain. This cooling chamber comprised of temperature controller, which was processed by PSoC microcontroller. Subsequently, those sensing and microcontroller devices will be interfaced to the liquid crystal display

(LCD)-system for temperature display. This direct brain cooling system was registered as D-Brain Cooling Machine™. Figure 1 illustrates the details.

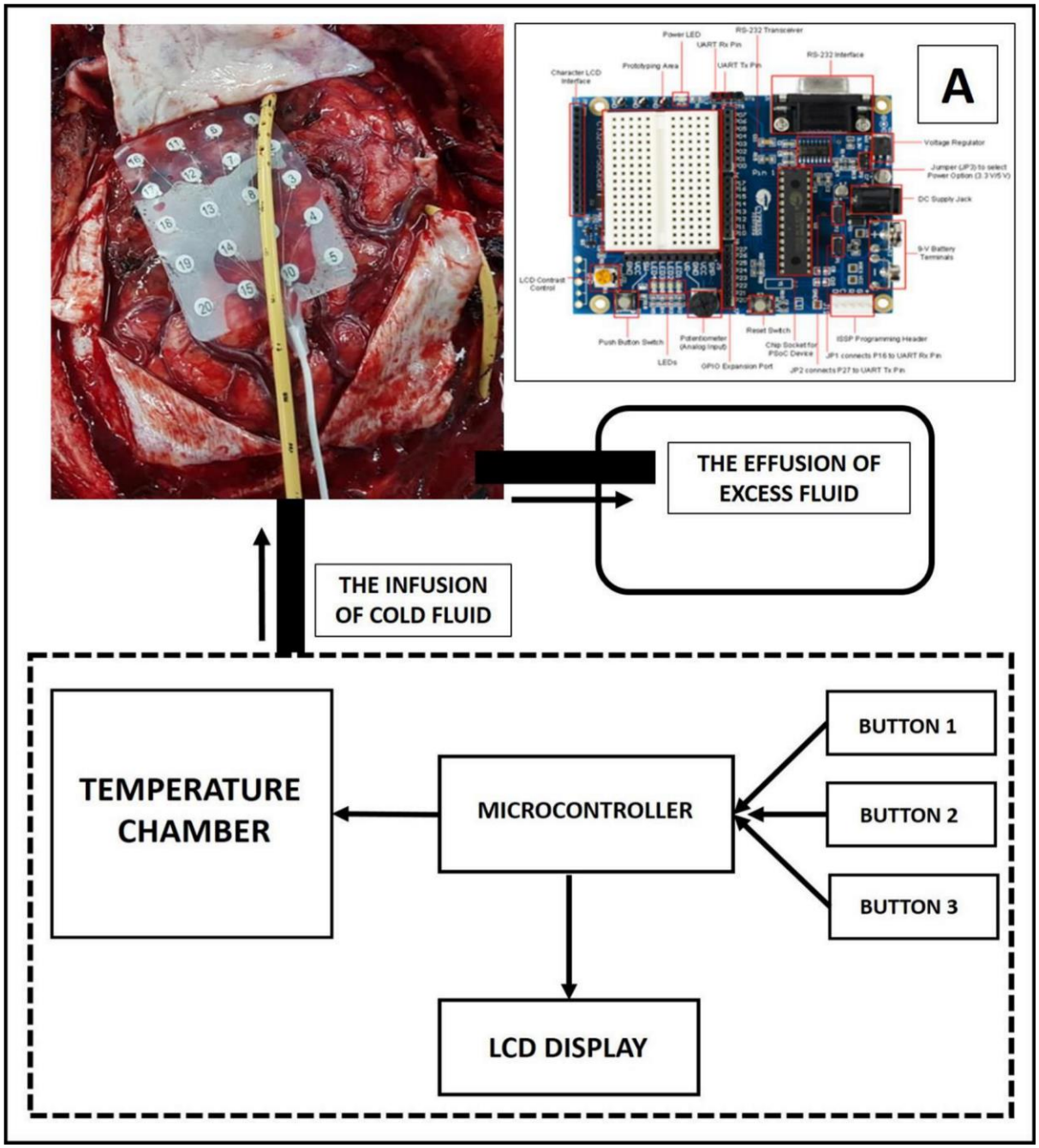


Figure 1. The direct brain cooling system with its principles. The inset (image A) is the Cypress PSoC 6 microcontroller CY8CKIT-062-BLE.

Part B

The second part of this study is to investigate the effects of direct focal brain cooling on the outcomes, monitored parameters and human cortical brainwaves. A prospective randomized controlled study, which is designed to answer the research questions regarding the effect of direct focal brain cooling treatment by using a newly developed cooling machine in adults who had decompressive craniectomy for closed severe traumatic brain injury was approved by the research and ethics committee (Ethic No.

JEPeM/18010074). The patients were randomized to one of the two-treatment arms: cooling (Group A) versus no cooling (Group B). Sealed envelopes, initially blinded to both consenting individuals (on the patients' behalf) and clinicians, containing either paper A (for cooling group) or B (for no cooling group) were randomly chosen. A total of 41 envelopes were used, which were equally divided between A and B group. In regards to blinding to the therapy, there was no blinding done after assignment to the interventions. In summary, group A (cooling group) consisted of severely head injured patients (GCS 3-8) who had therapy with direct focal brain cooling, whilst group B was the control group (also severely head injured patients with GCS 3-8). All patients had ICP, Licox (focal brain oxygenation and temperature by Integra, Mielkendorf Germany) and electrocorticography (ECoG) monitoring (NicoletOne^{TM} System, Natus Neurology Incorporated Middleton, USA) (Figure 2). The overall monitoring and therapy period lasted for 48 hours.

The neurosurgical decompressive craniectomy operation was a standard operation covering the frontal, parietal and temporal lobes. For the intracranial pressure probe, its insertion into the ventricle or parenchyma of the brain was made. For the Licox probe, an abnormally looking brain area was selected during the surgery for its probe insertion; and for the ECoG grid, it was laid onto the surface of the decompressed brain. The ECoG brainwave monitoring was made using either an 8x4 or a 5x4 grid of a NicoletOne^{TM} System with adjustable sensitivity format ranging from 10 to 5000 uV/cm, time-based of 30 mm/sec as well as with low and high cut of 1 and 50 Hz. The power or energy (uV^2/Hz) of the brainwaves was automatically calculated by the Quantitative ECoG (qECoG) Power band-software in the NicoletOne^{TM} System. The brainwave frequency analyzed in this study was limited to the range between 1 to 50 Hz. The monitoring and therapy given after surgery were the standard therapy for severely head-injured patients – these include sedation (propofol 10mg/hr and fentanyl 50 mcg/hr) without muscle paralysis agent; ventilator support; draining of cerebrospinal fluid (CSF), hypertonic saline or mannitol; and finally thiopentone coma therapy (for those with stable vital signs) for the persistent increase in intracranial pressure (refractory ICP) of more than 20 mmHg. Direct focal brain cooling method was completed through continually irrigating the brain with cold Hartmann's solution via the newly innovated system as described above. The temperature of the infused fluid was made constant at 32°C throughout the treatment period. Owing to the patient's head position setting in the neurointensive care unit, a second larger draining tube was inserted at the lower part of the craniectomy

flap outside the dura, which was loosely closed to drain the excess fluid with a low suction pressure. For the control group, no cooling therapy was given. Nonetheless, all controlled patients were also monitored with the ICP, Licox and ECoG grid. The assessment of the outcomes was performed through a dichotomized Extended Glasgow Outcome Scale (GOSE) at discharge and at 6 months after trauma as (a) good neurological outcome group (GOSE 4 to 8), and (b) poor neurological outcome group (GOSE 1 to 3). The statistical analysis was completed using Statistical Package for Social Sciences (SPSS; IBM, Chicago, Illinois USA) version 23.0. The level of statistical significance was set at $p < 0.05$.

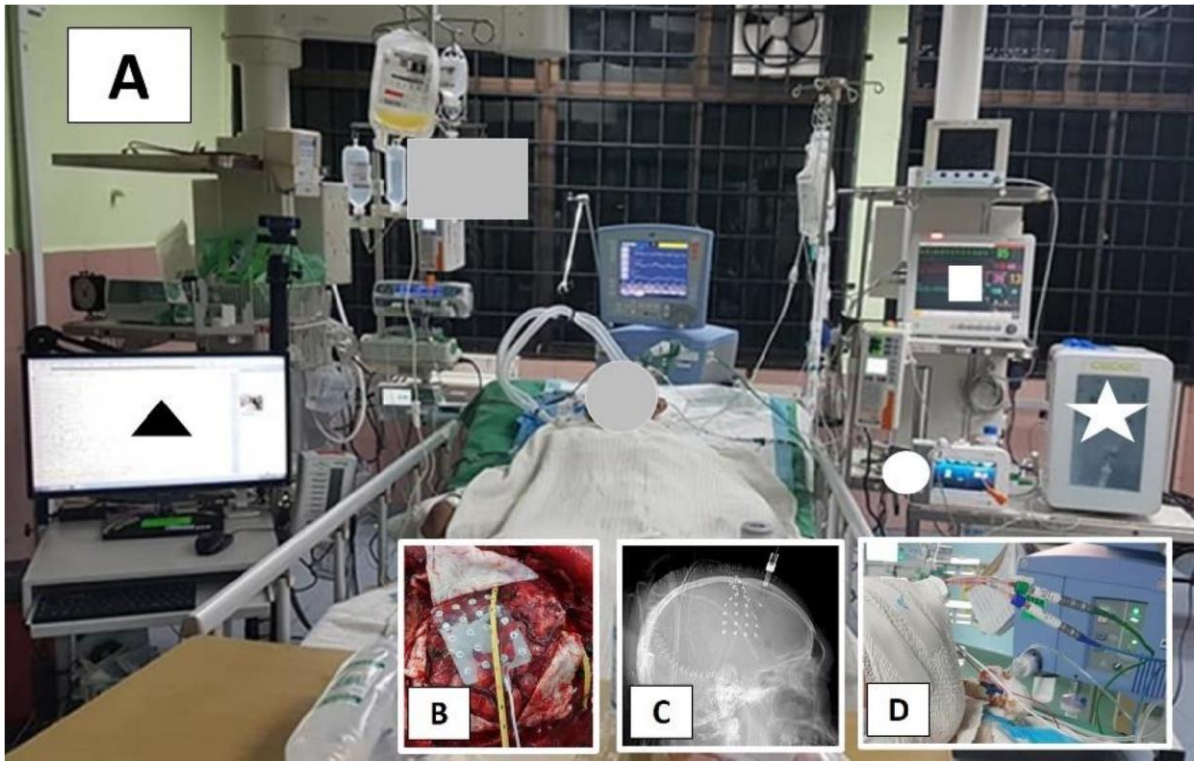


Figure 2. Direct brain cooling therapy and monitoring for severely injured brain. A: the neurointensive setting with cooling machine (white star), Licox brain oxygenation and temperature (white circle), ICP and CPP monitor (white rectangle), and cortical-brainwave monitoring (black triangle). B: The grid electrode was laid onto the injured brain and a cooling catheter was sutured to the inner dura. C: The postoperative skull radiograph shows the Licox probe and ECoG inside the skull. D: The external features of wirings for all monitoring probes.

Results

The results are divided into Part A and B. Part A explains further details on the direct brain cooling system, while Part B contains the results of clinical feasibility, effectiveness and safety of the system, including some case examples depicting brainwave changes in cooling, non-cooling and dead patient.

For Part A: The Direct Brain Cooling System (The D-Brain Cooling Machine™)

The innovated system consists of three main components: 1) the temperature selection and microcontroller system; 2) the automation of fluid flow control rate; and 3) the effusion tubing. For the selection of temperature sensor and integration with the microcontroller system, the selected temperature sensor was based on its temperature range, accuracy and resolution. In pertaining to this project, the chosen temperature range was between 25 – 40°C, which was based on our previous background study, whilst the accuracy and resolution for temperature sensor were +/-0.25% and 0.1°C, respectively. In this project, two types of temperature sensors were selected: the temperature sensor for the chamber and the temperature sensor for the fluid inside the irrigating tube before reaching the brain. For chamber temperature monitoring, a thermocouple temperature sensor was selected to control the chamber temperature environment. In relation to this, the PSoC 6 microcontroller (CY8CKIT-062BLE) will convert the thermocouple reading to temperature digital displayed reading. For fluid temperature, an infrared-based temperature sensor MLX90614 from Melexis was selected in this project. The sensor was clipped on the tubing at the outlet chamber as depicted in Figure 3A. This particular sensor ensured only fluid with fixed temperature was allowed to be drained to the treated brain after turning on the automated flow control button. For the automation of flow control rate, this system was implemented with a stepper motor to control the flow rate. The stepper motor operation will be determined by PSoC microcontroller system. Thus, the investigator needs only to set the fluid flow rate for it to work. For the fluid effusion tubing system, the effusion tube from the machine was connected to the ventricular brain catheter, which was inserted at the roof or upper part of the incised inner dura, so that the coolant (cooling fluid) was bathed onto the injured surface of the brain cortices and subsequently into the cerebrospinal fluid (CSF) cisterns. By irrigating into the CSF cisterns, hopefully, the coolant would

also be redistributed to the whole brain through the mechanism of brainvascular pulsation. Finally, the Engineering-laboratory in vitro testing was made at Collaborative Microelectronic Design Excellence Center (CEDEC). The clinical testing (Part B) proceeded after the electrical and mechanical characterizations were tested and accurate coolant temperatures were confirmed in vitro. A finished system is shown in Figure 3B.

Figure 3. A: An infrared based temperature sensor was clipped on the tubing at the outlet. B: The finished direct brain cooling system viewed from the front, side and back.

For Part B: Demographic data of patients included in the study and their outcomes

A total of 41 patients were available for analysis in the intention-to-treat. There were 10 patient in cooling group, while 31 patients in the control group. There were 36 males and 5 female, with nearly equal gender in each group. The mean age of the recruited patients in the cooling group was 25, and 36 for the control group. Other basic and important comparing parameters were found to be insignificant for the GCS, Marshall CT grading score and trauma severity score. This suggests that the studied groups were comparable. Our data demonstrated better Extended Glasgow Outcomes Scale (GOSE) in the direct brain cooling group at a fixed temperature of 32°C than in the control group with significant p values at the time of discharge ($p = 0.001$) and at 6 months after trauma ($p = 0.015$). Surprisingly, there was no difference in the monitored parameters for ICP, CPP, brain temperature and focal brain oxygenation. However, there were obvious inclination towards lower ICP values, higher CPP values. Finally, in this particular study, there was no major complication noted in all of our alive studied patients. Table 1 and Figure 4 depict the findings that were stated above.

Table 1. Baseline demographic, monitoring and outcome data.

	Direct Brain Cooling (A)	Control Group (B)	P-value (Anova test)
Total No of Cases	10	31	
Age (mean in years) (95% CI)	28.1 (20.91-35.91)	30.5 (24.56-36.68)	0.687
No of Male Gender	8	28	
No of Female Gender	2	3	
GCS (median) (95% CI)	6 (4-7)	6 (4.5-7)	0.811
Marshall Score (median) (95% CI)	4 (4-5)	4 (4-4)	0.255
Trauma Severity Score (95% CI)	30 (27-34)	27 (27-35)	0.584
Mean ICP (mmHg) (95% CI)	**13.27** (9.44-17.26)	17.11 (13.87-20.4)	0.207
Mean CPP (mmHg) (95% CI)	**66.84** (63.09-70.92)	63.58 (59.22-67.89)	0.407
Mean Focal Brain Oxygenation (mmHg) (95% CI)	28.11 (**22.4-33.48**)	27.24 (11.86-43.05)	0.907
Mean Brain Temperature (°C) (95% CI)	36.21 (**35.08-37.22**)	34.89 (32.18-37.28)	**0.350**
Median GOSE at discharge (range)	3 (2-4)	2 (1.5-2)	**0.001**
Median GOSE at 6 months (range)	4.5 (3-5)	2 (1-3)	**0.015**

Complication in alive patient (pneumonia, thrombosis, arrhythmia or wound infection)	None	None	

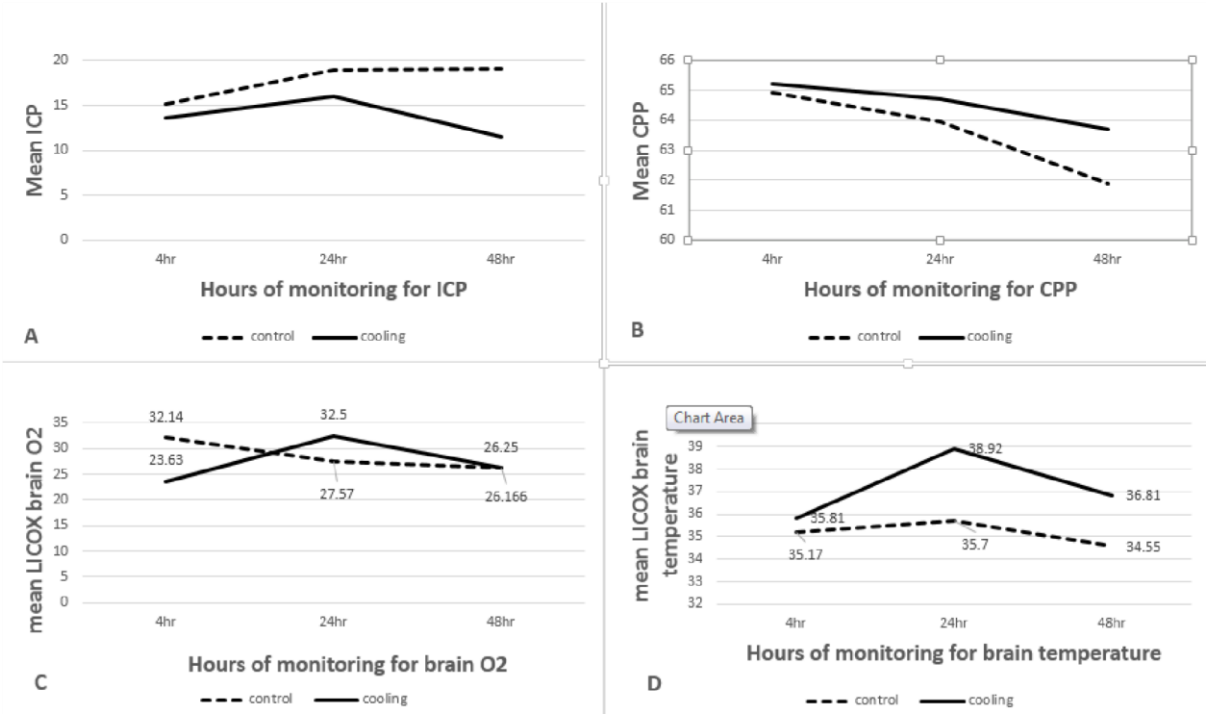


Figure 4. Trends for the monitored parameters over 48 hours period. A: The cooling group had lower mean ICP values than the control group (< 20 mmHg). B: The cooling group had higher mean CPP values than the control group. C: The cooling group had mean focal brain oxygenation within range of 24 to 34 mmHg, with the ascending trend within the first 24 hours of therapy; on the other hand, the control group has a wider range of 25 to 40 mmHg. D: The focal cortical brain temperature was higher in the cooling group with values range from 36.36 to 36.93°C.

Abnormal epileptic activity detected on electrocorticography and case examples of brainwaves pattern in cooling, non-cooling and dead patient

Other interesting finding noted in this series of patients were the presence of cortical brainwave abnormalities in all of our studied patients. The abnormalities were noted after the surgery and prior to any given therapy in intensive care. The noted abnormalities were a form of abnormal epileptic activities, such as spikes, spike-waves, sharpwaves, polyspikes and slowings. They tend to appear periodically and may evolve into a burst of high energy waves. Figure 5 depicts the typical

morphological features of abnormal cortical brainwave patterns that were present in our studied patients. With these findings, we present three case examples that had abnormal ECoG and were in the cooling and non-cooling group. The last presented case is a fascinating one - as shown in the ECoG findings during his noted transitional period from being alive to dead.

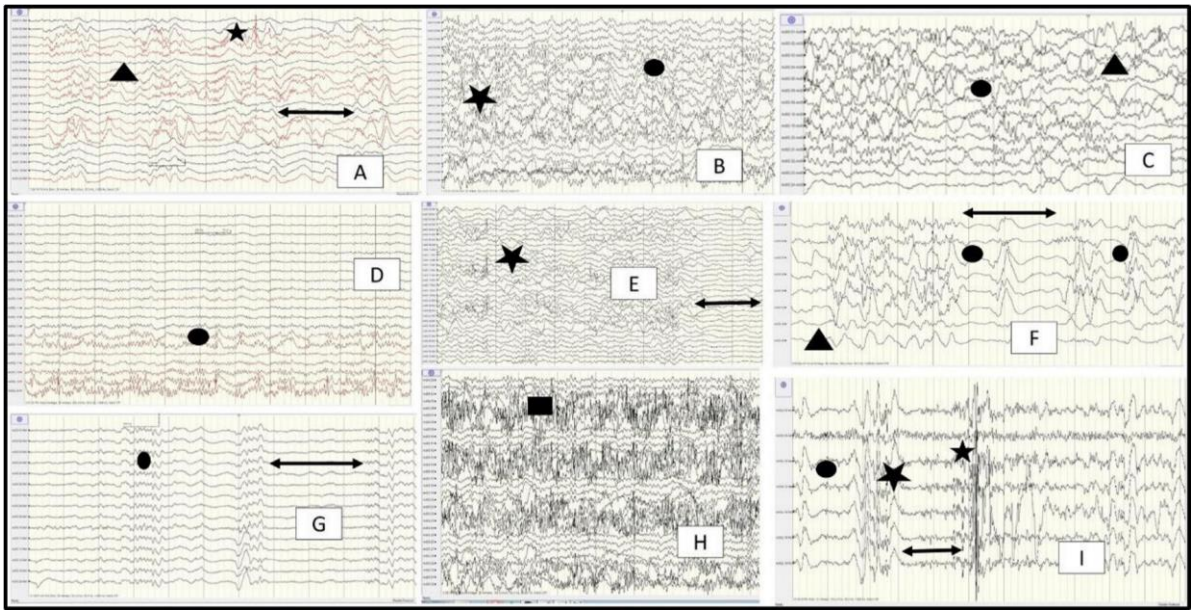


Figure 5. Severe traumatic brain injury is noted to be associated with significant brainwave changes. A-I images represent different patient electrocorticographic images captured immediately after the decompressive craniectomy. The noted abnormalities include spikes and spike-waves (black star), sharpwaves (black circle), polyspikes (black rectangle), slowings (black triangle) and the arrow indicates the periodic pattern of discharges in most of the cases. The epileptiform patterns tend to occur singly or in bursts lasting in seconds or even longer. The abnormal brain areas, such as contused and ischemic brain areas tend to give rise to these abnormalities.

1) A case demonstrating cortical brainwaves of a direct brain cooling patient

A 23-year-old man was involved in an alleged road traffic accident. He sustained GCS of 5 with CT brain revealed effaced basal cisterns suggesting brain swelling, presence of right-sided 1.5 cm maximum thickness of an acute subdural hemorrhage (SDH) that caused a midline shift to the opposite side for about 1 cm. He was operated urgently in which a decompressive craniectomy was performed, subdural hemorrhage was removed and duraplasty was made. The insertion of Licox and ICP probes, laying of the cooling and drain-out catheters and the subdural grid electrodes were made at the end of

the surgery. The patient was treated with our newly innovated direct brain cooling system at a fixed and constant temperature of 32°C for 48 hours. The therapeutic hypothermia at 32°C causes higher brain oxygenation and reduces abnormal epileptiform discharges (subclinical seizures). The results are depicted in Figure 6. The patient was extubated and was discharged home after inpatient rehabilitation. The 6 months GOSE was 5 (lower moderate disability) in which the patient is able to live independently, rarely participates in social activity and does suffer from a psychological problem (memory disturbance).

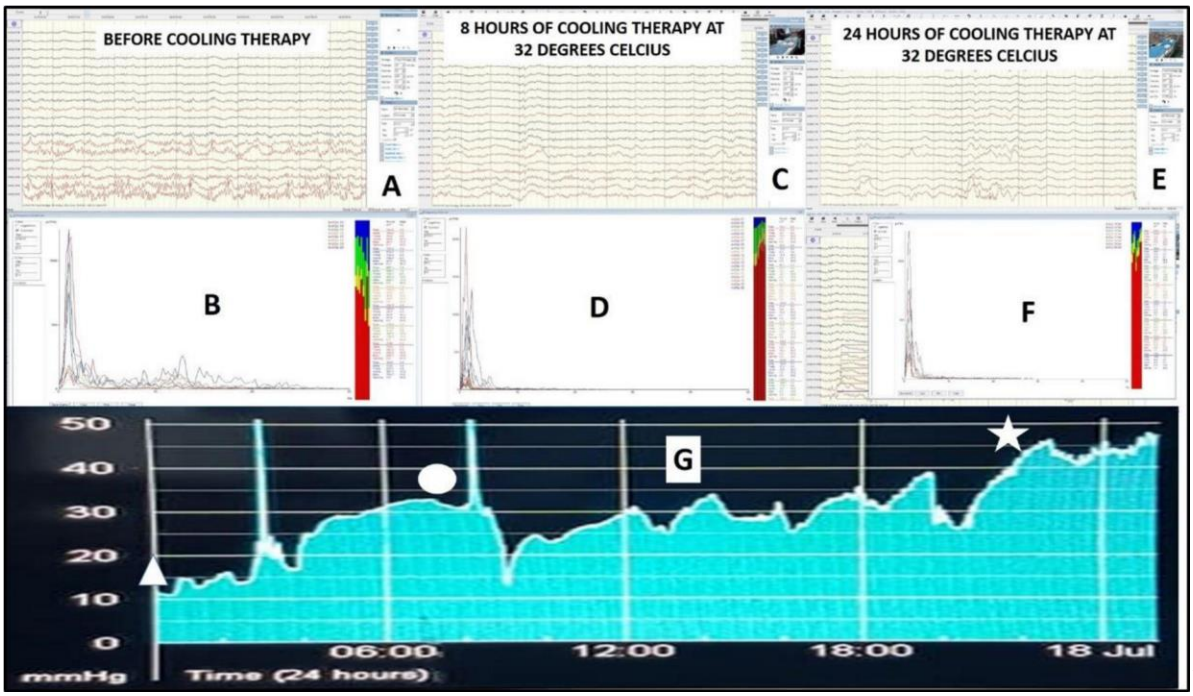


Figure 6. The effect of direct brain cooling on brainwaves and brain oxygenation. A, C and E: The cortical brainwaves show improvement from having frequent spikes and sharpwaves to only slowings when receiving direct brain cooling therapy. B, D and F are the power (uV^2/Hz) or energy consumption for A, C and E, respectively. The energy consumption appears progressively less with obvious reduction in the alpha (green) and beta (blue) bands as the duration of cooling is longer. These improvements are in line with the marked elevation in brain oxygenation (G) noted from time of cooling to the first 24 hours (G or for the brain oxygenation level: white triangle – at the time to start cooling, white circle – at 8 hrs of cooling, and white star – at 24 hrs of cooling).

2) A case depicting the cortical brainwaves of non-cooling patient

A 26-year-old man was involved in a road traffic accident and sustained GCS of 6. The initial CT brain disclosed a brain swelling, an acute SDH with midline shift to the opposite side of 1 cm. He was operated urgently and in a similar fashion to the description made above for the cooling patient. The only difference was no cooling catheter was laid onto his exposed and decompressed brain. Despite the standard dose for the sedation and prophylactic antiepileptic medications, the abnormal epileptiform discharges or subclinical seizures were still present as regularly seen on our direct cortical brainwave monitoring. The results are depicted in Figure 7. These subclinical seizures, which were noted as difficult to be put under control may perhaps be best treated with the resection of the seizure focus. Obviously, if without this type of monitoring (ECoG), the clinician will not realize the presence of this gross brainwave abnormality. This patient finally succumbed to death (GOSE 1) on the 4th day after trauma.

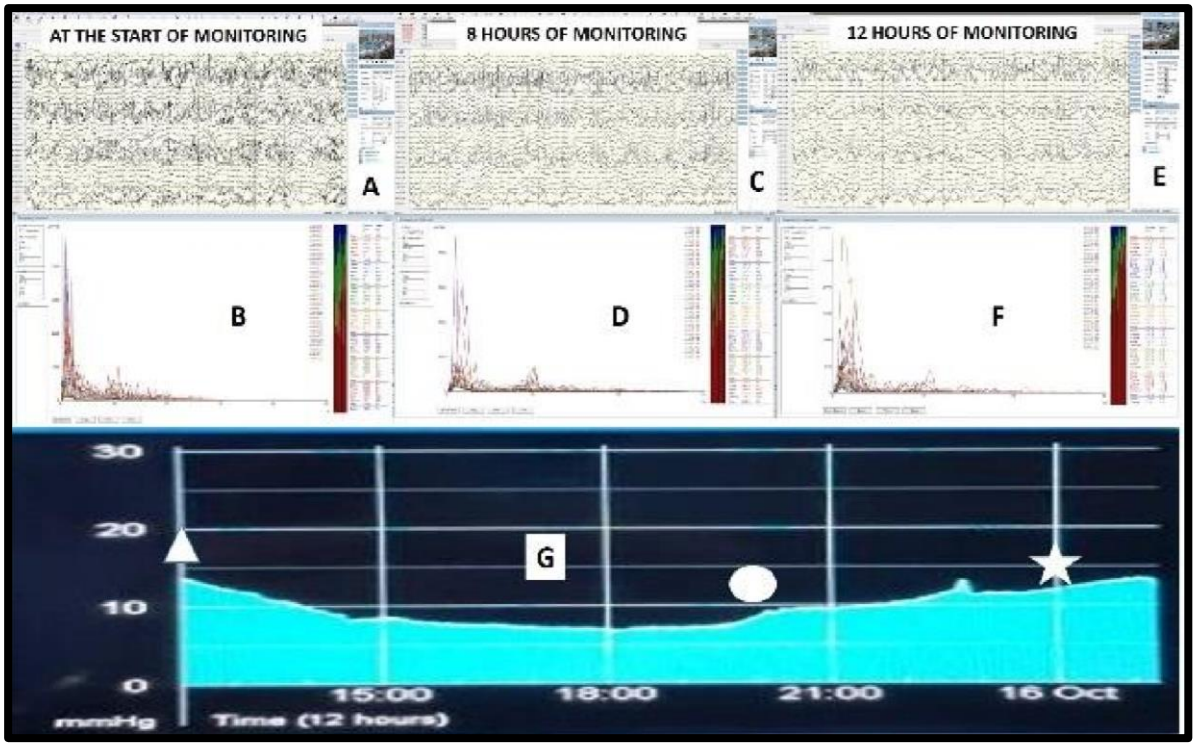
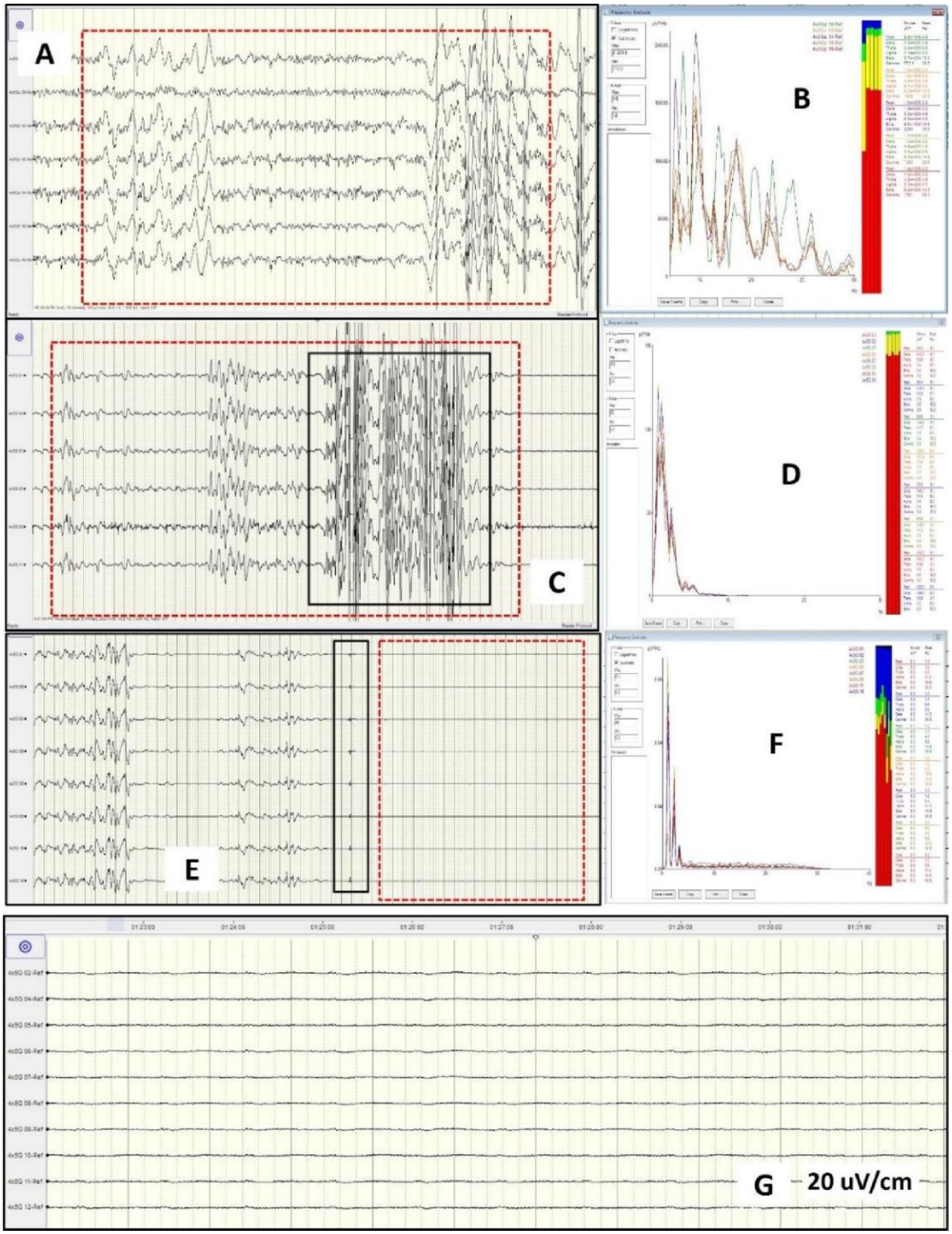


Figure 7. Non-cooling patient with abnormal epileptiform discharges (subclinical seizures). A, C and E are the abnormal brainwaves, which persisted throughout the monitoring period. Similarly, the energy consumption for respective brainwaves (B, D and F) show high level of energy usage. G: The brain oxygenation level shows much lower values for this non-cooling patient (For the brain oxygenation level: white triangle – at time to start the cooling, white circle – at 8 hrs of cooling, and white star – at 12 hrs of cooling).

3) A case illustrating a transition in cortical brainwaves from being alive to dead

This is another patient who was randomized into the non-cooling group. He was a 34-year-old man, sustained a road traffic accident with an initial GCS of 5. He had brain swelling and an acute SDH. He underwent decompressive craniectomy and removal of the surgical lesion. Despite the surgery, he succumbed to death 3 days after the surgery (GOSE 1). His cortical brainwaves disclosed peculiar features of wave-transition from being alive to dead. As depicted in Figure 8, the sudden energy burst and a gradual shift to lower power brainwaves were noted at the transitional period. Other fascinating features are the presence of wave coherence in all cortical lead electrodes and the presence of gamma waves (>40 Hz) with background miniature oscillations at the flattened or isoelectric part of the waves.



Note: The quantitative ECoG (qECoG). Image B, D and F: For the graph - the absolute bandpower [energy/power in uV^2/Hz] of the brainwaves is in the y-axis and wave frequency is in the x-axis. The red boxes represent the original brainwaves that were analyzed for the power or energy consumption (uV^2/Hz). For the colored spectrum – it represents the relative bandpower of brainwave spectrum i.e. red for delta, yellow for theta, green for alpha, blue for beta and black for gamma.

Figure 8. The sudden burst pattern before dying. A: alive pattern. B: alive with intact oscillation of brainwaves with multiple peaks (qECoG). C: Burst pattern (rectangular black box). D: Energy burst

with homogenous and more coherence brainwave oscillations (with few multiple peaks) (qECoG). E: from burst to gradually flattened brainwaves with final spikes (rectangular black box); Do note that the C and E brainwave images were taken not far apart. F: The measured energy or power when the brainwaves became isoelectric (qECoG) – note the presence of background gamma waves (black/above the blue spectrum). G: A hidden hypothetical quantum field energy may give rise to the background tiny oscillations as noted in the G-image when the direct cortical brainwaves sensitivity-view was increased to 20 uV/cm (i.e. the largest waves/per scale image).

Discussion

1) A Newly Developed Direct Brain Cooling System

Therapeutic hypothermia is commonly achieved by several possible methods. The first option is via an external cooling system, such as wrapping a patient with a blanket (or pad) in which cold liquid (or air) circulates or via a cooling helmet. They are possible but with some disadvantage, such as skin reactions, local tissues damage and their indirect method in the cooling technique (Polderman 2004b; Polderman and Herold 2009; Delhaye, Mahmoudi, and Waksman 2012). The second option is via an endovascular cooling system, cold systemic infusion or extracorporeal circulation system. The drawbacks of these second method are their invasiveness, thrombosis and systemic infection complications, which again the method is indirect (Polderman and Herold 2009; Flint, Hemphill, and Bonovich 2007; Kliegel et al. 2005; Simosa et al. 2007). In 2014, our group published a focal and direct method of cooling to the injured brain (Idris et al. 2014). The cold Hartman's solution was infused through a catheter, which was laid onto the surface of the decompressed brain. It is feasible because the severely injured brains commonly required decompressive craniectomy in trauma. Nonetheless, this technique did not offer a convenient and accurate way in temperature measurement of the infused fluid during the whole process of the irrigation. Therefore, further improvement was made by using our newly innovated direct brain cooling-machine system. With this system, a selected temperature was maintained and the right rate of the infused fluid was made possible. The system used the miniaturized PSoC microcontroller technology with an adjustable temperature chamber that was interfaced to the LCD-system display. Thus, the system offers an ideal way to administer cooling therapy to the brain by continuously irrigating the injured brain with a fixed amount of fluid and at a constant temperature set-up. The method was named as a direct brain cooling simply because of the coolant fluid that goes directly into the skull. This direct cooling method was thought as not only cooling the region of interest but also other brain areas that are far beyond the irrigated area through the vascular-brain pulsation which is commonly enhanced in any injured and compensated brain (Idris, Mustapha, and Abdullah 2014; Kim et al. 2015, 2016).