Surgical management by means of electroretinographic examination during Extracorporeal Circulation

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Surgical management by means of electroretinographic examination during extracorporeal circulation.

BACKGROUND: *Neurological and/or neuropsychological damages are important complications of cardiosurgical interventions. This study determined if the timing of the electroretinographic (ERG) ocular exam can assess intraoperative brain damage of patients supported by extracorporeal circulation (ECC) during cardiosurgical interventions.*
MATERIALS AND METHODS: *The authors illustrate an ERG technique being able to evaluate on 12 patients during cardiosurgical interventions and in conditions of ECC, both hypothermic and normothermic, the possibility to forecast the potential neurological and/or neuropsychological damages.*
RESULTS: *The ERG waves obtained are compared before and after ECC in various conditions of corporeal temperature. During ECC all patients had a change of ERG waves, whom was particularly significant for patients operated in conditions of induced hypothermia.*
CONCLUSIONS: *The observations reported by ERG provide new and important information in support of the potential organic suffering. This exam can assess the defect of the waves indicative of insufficient ocular and brain perfusion of patients supported by ECC during cardiosurgical interventions.*

KEY WORDS: Cardiopulmonary Bypass (CPB), Cardiosurgical Interventions, Electroretinogram (ERG), Extracorporeal circulation (ECC), Postpump syndrome.

Introduction

The cardiosurgical interventions, such as valve replacements and aorto-coronary or cardio-pulmonary bypass (CPB), are at high risk of complications involving the central nervous system (CNS) and the damage that may result causes the so-called *Post-Pump Syndrome (PPS)*. The incidence of complications increases after the age of 70 and especially in cases where there is a lack of self regulation of cerebral blood flow as well as in patients with metabolic disorders.
Furthermore, the postsurgical kidney, intestine, lung, eye complications can occur in both the short and long term [1-3]. The main causes which can determine the onset of the described damage are due to:
– Cerebral embolism (biological or gaseous);
– Organ infarction after endothelial damage, platelet aggregation or release of coagulation factors [3,4];
– Systemic hypoperfusion due to accidents during the extracorporeal circulation (ECC);
– Inflammation factors present in the circulation such as polymorphonuclear leukocytes or metalloproteinases [5,6].
The CNS dysfunction after cardiac surgery can be dis-

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tinguished in an exclusively neurological form (stroke, hemiplegia, epilepsy, etc.) that can account for up to 5%, and a neuropsychological one, which may account for up to 35% of treated patients.

While mortality from heart disease after valve replacement and coronary artery bypass surgery has dropped to about 5%, that due to neurological causes raised to almost 10% [1,2,7].

The surgery following acute type A aortic dissection, according to Stanford, has a fatality rate of 50% in the first 48 hours after surgery and the intra-operative mortality raging from 12 to 28% [8-14].

We know that temperature is the main factor which determines the cerebral metabolic kinetics, as there is a 7% reduction of cerebral metabolism for each reduced degree of temperature.

Hypothermia reduces the cerebral protection, as it acts on both homeostatic and electrophysiological cellular energy expenditure [15-18].

It is impossible to predict for each patient a safe level of cerebral perfusion pressure during ECC which may be followed by unexpected states of hypoperfusion, induced by several factors: hemodilution, vascular embolism, mediators of inflammation, anesthetics used etc.

Studies by Bietti and Scano [19] in 1946 showed how during CNS hypoperfusion alterations of the retinal circulation can be early predictors of brain damage.

In World War 2 fighter aircraft pilots accused bilateral amaurosis before loss of consciousness due to sudden deceleration of their aircraft. The rapid regression of deceleration was followed by a rapid visual recovery without loss of consciousness. This cascade of events was reproduced by an experimental spin on healthy individuals and it would be attributed to the shift of blood volume to the sloping areas of the human body. This artifice would simulate a condition of cerebral hypoperfusion similar to that which would occur during the intraoperative phase of ECC [19]. Different cerebral monitoring techniques were compared with the retinal circulatory system as this is supplied by the internal carotid artery and the eye has a blood-retinal barrier complementary to the cerebral one [3,19,20].

After considering the inadequacy of the various techniques (Table I) we decided to use the Electroretinogram (ERG) during CPB operations.

The aim of our work was to study a new technique able to determine ahead of time the incidence of morbidity and mortality from neurological dysfunction post-heart surgery in cases of ECC. One will study the ocular neural models that seem to represent the most sensitive system capable of an early assessment of the likely future damage on the brains organic potentials after the surgery.

Materials and methods

Twelve patients, 8 males and 4 females, with a mean age of 65.7 ± 8.3 years were treated with CPB. In compliance with the Helsinki Declaration, an informed consent was obtained from all subjects before enrolment. 8 were operated under conditions of moderate hypothermia (28-30°C) and 4 under conditions of normothermia. Patients with previous cerebrovascular or CNS dis-

TABLE I - *Diagnostic investigations during Cardiopulmonary Bypass (CPB) operations.*

Technique	Benefits	Disadvantages
Central Retinal Artery Echo-color-Doppler (CRA) After aortic arch clumping retrograde cerebral perfusion (subclavian)	Highlights the retrobulbar blood flow through collateral circulation by the Circle of Willis	Useless for lack of pulsatility of the CRA and low perfusion pressure
Retinal Angiography Similarity between retinal and cerebral circulatory changes	Detects: Filling defect, retino-choroidal leakage, ischemic areas	Expects a pulsed blood flow, the contrast dye is removed in minutes
EEG	Common use	“Slowing” type reduced and/or increased in amplitude signal
Transcranial Doppler	Examines the velocity of blood flow in basal cerebral arteries	Values differ significantly from those obtained with the technique of Kety-Schmidt
Clearance of the radioactive isotope: Xenon 133 Introduced by air or carotid or i.v.	Similar results to those obtained with the technique of Kety-Schmidt	Exposes the patient to high doses of radiation

ease, diabetes mellitus, eye diseases have been excluded. Before induction of anesthesia, patients were conventionally monitored: ECG recording, systemic blood pressure using radial artery cannulation, central venous pressure, oxygen saturation, capnography and the hourly diuresis.
The induction of anesthesia was achieved with fentanyl 7μg /kg and midazolam 0.1 mg / kg. After endotracheal intubation, patients received controlled mechanical ventilation. Body temperature was measured continuously via a rectal and a nasopharyngeal probe. The average duration of surgery was 3:34 ± 0.34 h, the average time of ECC 92.5 ± 8 minutes, and the clamping of 74.2 ± 7 minutes.
For the ERG recording a Conel computerised equipment supplied with a 12-bit AD converter and an interface card for connection to a biological amplifier preceded by a two-channel preamp with a total amplification of 5000 was used. Both channels of preamp were connected to amplifiers through photoelectric coupling, to ensure an insulation voltage greater than 5 KV. The bandwidth for the ERG channel was used from 0.3 to 1500 Hz.
A silver chloride DTL (Dawson-Trick-Litzkow) fiber *exploring* electrode was applied in the eye of the patient and secured to the two canthi, nasal and temporal, with biological adhesive and after thorough skin cleansing. Two self-adhesive electrodes were in such way positioned: the *reference* in the center of the forehead and the *neutral* or *ground* in the mastoid ipsilateral area of the patient's explored eye.
The eye of the patient was in miosis induced by anesthesia and with closed eyelids, while the strobe light sent the stimulus through an optical fiber, FORT optical fibers, 2 meters long and 30 mm wide positioned at 2 cm from the eye. The stimulator was set to get a stronger flash light than standard. To control the background noise the recording of each ERG track started thirty seconds before the stimulus.
The first examination was performed before surgery and then repeated continuously, analyzed by software, displayed on a monitor and stored on a CD-Rom.
Samples with high noise obtained during the use of electric cautery were automatically outcast.
The algorithm of the averaging related was used to extrapolate the trace from background noise. The ERG can record changes of action potentials of the various retinal elements when they are subjected to light stimulus of high intensity and short duration [21].
The graphical representation of an ERG trace consists of a series of waves whose peaks may be divided for a careful study of the components that generate the responses (Fig. 1). The characteristics of a ERG trace are defined by morphology, amplitude measured in μV and implicit time measured in ms (Fig. 1). In particular the A and B waves are the result of the activity of photoreceptors and OP waves or Oscillatory Potentials represent amacrine and horizontal cells that modulate nerve impulse [21]. The photoreceptors are supplied by the internal carotid artery through the choroidal circulation while bipolar and amacrine cells from retinal microcirculation. The glial cells: Muller, Astrocytes, Microglia and perivascular Glia are distributed in the innermost layer of the retina and their functions are support, tropism, homeostasis and metabolism for all retinal components. All retinal cells are affected by the quality and quantity of blood flow and hence perfusion pressure and hemodilution, which can persist for days after surgery.

Results

In the 12 examined patients there were no changes in ERG examinations from the beginning of anesthesia until the start of the ECC. Instead from the beginning of the ECC there was a reduction of amplitude, increased

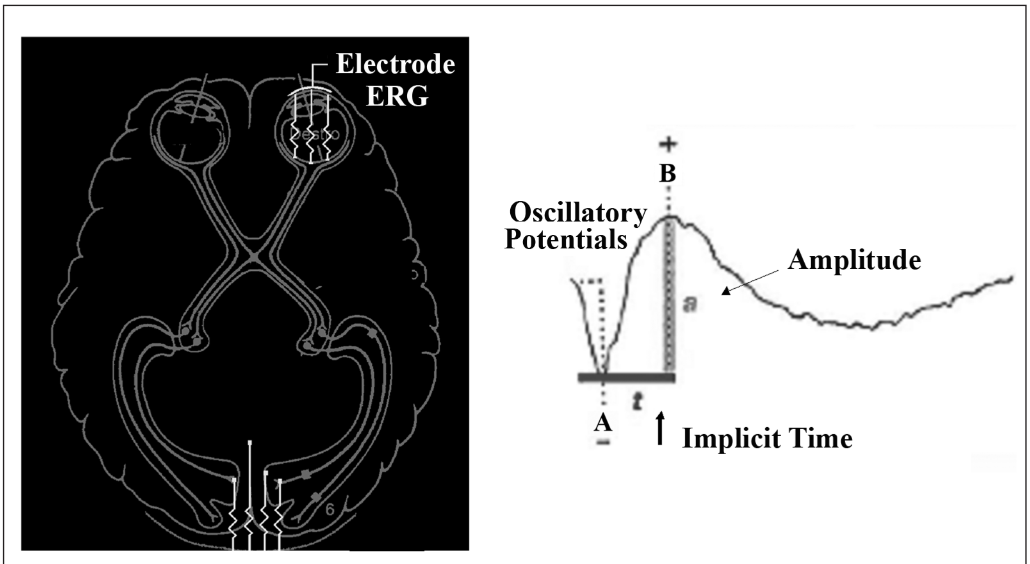

Fig. 1: Stimulation with light or contrast activates the retina-cortex visual system. This causes the emission of intra- and extra-bulbar currents, which can be detected with extraocular electrodes.
On the right the characteristics of an ERG waves: morphology, amplitude and implicit time.

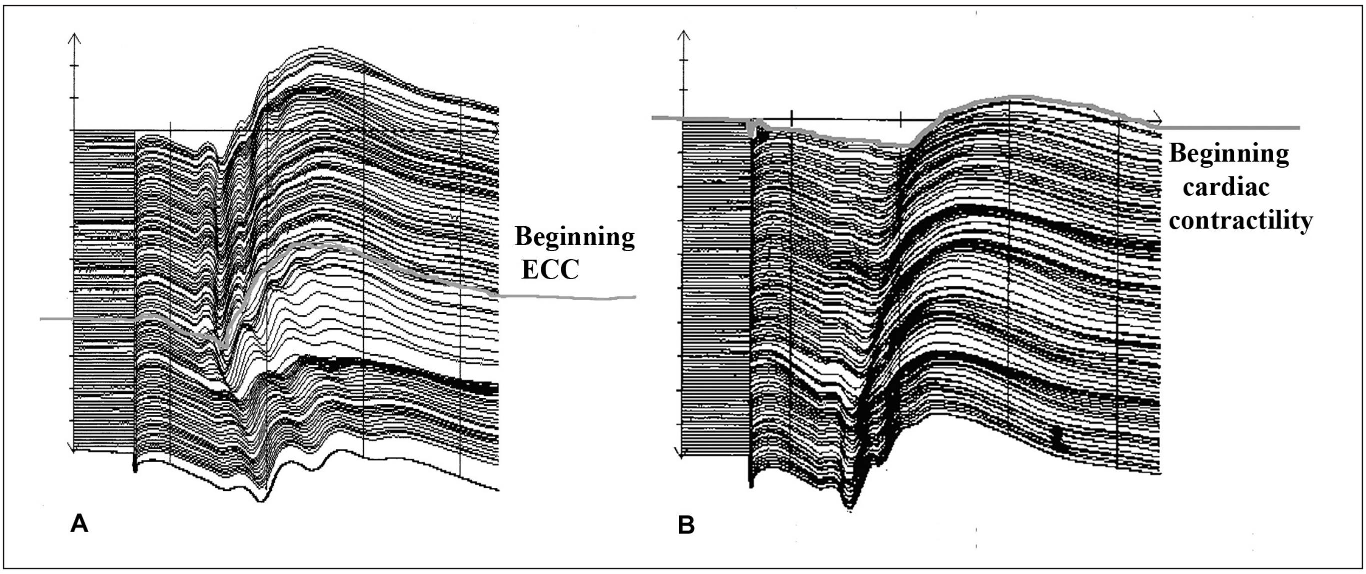

Fig. 2: (A) Amplitude reduction of about 50%, increased implicit time and morphological variation of the ERG track in patients in whom hypothermia was induced during ECC; (B) Immediately after the warming up phase and the recovery of cardiac contractility the graph almost returned to its baseline.

implicit time and a morphological change of the trace, especially in patients in whom hypothermia was induced. In the latter there was a decrease of about 50% (Fig. 2A), while patients in normothermic conditions had a reduction of the baseline trace of only 10%. The trace, with reduced amplitudes, remained so until the warm-up phase and the recovery of cardiac contractile activity. In fact immediately after the chart almost returned to baseline values, but anyway not more than 90%, in the first hour after the operation (Fig. 2B)

The variation in the A and B waves show the qualitative alteration of retinal blood flow due to hemodilution, which is used to reduce the harmful effects caused by increased viscosity due to temperature reduction. Hemodilution may be responsible for the low doses of hemoglobin, which are correlated with an eventual ischemic insult that results in a functional block of photoreceptors due to tissue hypoxia.

Changes of the OP, where the track flattens out up to 50% of the baseline, indicate both a reduction in quality and quantity of blood flow and therefore a neuronal and glial cell functional reduction or block.

Warming the patient and resuming the rhythmic cardiac activity will restore the PO reflecting a temporary reduction of cell activity and not a permanent damage. So ERG changes for variations in blood flow, continuous and not pulsed, followed by a reduction in perfusion pressure, for hemodilution and for temperature reduction. This leads to a reduction in neuronal metabolism and depresses cell function and therefore the energy requirements.

None of the patients experienced postoperative neurological deficits, but one of the patients suffered from a severe and prolonged hypotension for which a longer-term ventilatory support (18h) and a longer time in hospital in intensive care (48h) were required. In this patient at the end of the operation the ERG trace was not restored as in the other cases. The severe hypotension caused a marked hypoperfusion responsible of a structural and functional suffering of brain and retinal cells, but for a period not long enough to change their vitality and therefore not able to evolve into permanent damage, as demonstrated by the slower but complete postoperative autonomy recovery.

Conclusions

We know that one can measure the cerebral blood component of a hemisphere with various methods; the gold standard is the *Kety-Schmidt* examination (Table I). This is the analysis of the curves of saturation of a diffusible inert and insoluble gas in samples of arterial and jugular venous blood after inhalation [5,6,22]. This particularly complex method does not allow continuous information during surgery and also in the stage of hypothermia can lead to an overestimation of the measurement up to 25% of cerebral blood flow.

While the latest technique of *Infrared Spectroscopy* is based on the changes of infrared wavelengths that penetrate the skull and their transmission from the brain tissue through reflection. Thus one measures the relative concentration of oxy and deoxyhemoglobin through the tissue [23,24].

The ERG has proved to be sensitive to two key variables, such as:

– alteration of blood flow become continuous with a consequent reduction in perfusion pressure;

– body hypothermia, associated with hemodilution, which are able to depress neuronal function and thus the energy requirements necessary to protect the brain structures, but also responsible for tissue hypoxia.

Our study was aimed to propose a new method of monitoring brain function during heart surgery under conditions of ECC. In the examined patients we had none of the fearsome intra- and postoperative complications reported in literature [1-3,5,7-14].

It can be assumed that in people at higher surgical or individual risk one could use the ERG examination during hypothermic ECC as an evaluation parameter able to minimize the risk of PPS. The verification of the theoretical assumptions for an optimization of the prediction of intra- and postoperative adverse events should undoubtedly be studied in depth.

However, our newly introduced biomedical application studies are a significant experimental performance, suitable to bring contributions not only at a theoretical but also at a practical level for those adverse events which have a high incidence in cardiac surgery.

It will be essential to assess, through a careful follow-up, the short and long-term effectiveness not only of the intraoperative but also of the postoperative cerebral protection through ERG examinations and later with visual evoked potentials which we intend to deepen continuing our study on individuals in whom we will need to evaluate the brain perfusion index.

In conclusion, although the study was carried out on few patients, we can say that the method can be used in intraoperative timing in order to seize in an early stage an eventual central suffering during hypothermic ECC. This innovative and particularly advantageous technique does not interfere in any way with the surgical and anesthetic maneuvers nor with the use of other electrical appliances during surgery. Hypothermia protects the brain structures, but requires a higher perfusion pressure to maintain neuronal homeostasis.

The possibility of having a completely non-invasive easy to read method, which is able to assess real-time cellular function changes assumes a significant importance to prevent neurological damage from PPS in cardiac surgery [25, 26].

Furthermore the degree of sensitivity and specificity of the exam remains to be seen in situations where there is a pathological permanent change in cellular homeostasis.

Riassunto

OBIETTIVI: Gli interventi di cardiochirurgia sono ad elevato rischio di complicazioni a carico del sistema nervoso centrale. Ad oggi non esistono esami predittivi di possibile insorgenza di danno neurologico postchirurgico. I flussi circolatori, retinico e coroideale, del distretto oculare rispecchiano fedelmente quello cerebrale. Lo studio si propone di valutare il deficit ipossico, energetico e quindi metabolico del comparto retino-coroideale come indice indiretto di sofferenza cerebrale.

MATERIALI E METODI: Nello studio si utilizza l'elettroretinogramma (ERG), che è una tecnica di elettrofisiologia oculare in grado di valutare la funzionalità dei vari elementi cellulari retinici. La metodica è stata applicata su 12 pazienti sottoposti ad intervento di bypass cardiopolmonare (BCP) in condizioni di circolazione extracorporea (CEC) normotermica ed ipotermica.

RISULTATI: Vengono confrontati i tracciati ERG ricavati prima e dopo CEC nelle varie condizioni di temperatura corporea. In tutti i pazienti si è avuta durante CEC una variazione delle onde ERG, che è risultata particolarmente significativa per i pazienti operati in condizioni di ipotermia indotta.

CONCLUSIONI: I risultati ottenuti consentono di affermare la validità dell'esame utilizzato. Sarà necessario proseguire gli studi intrapresi su un maggior numero di pazienti al fine di validare e codificare un eventuale protocollo di uso comune per la tecnica oggetto di studio.

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