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Cerebrospinal Fluid Thermoimpedancemetry as a Method of Brain Diseases Diagnostics

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Introduction

A cerebrospinal fluid (liquor) study is of great importance for the diagnostics and treatment of many diseases including trauma and cerebrovascular pathologies. Liquor is a complex biological fluid, which contains proteins, erythrocytes, other cells (cytosis), and circulates permanently in the ventricles and subarachnoid space of the brain and spinal cord. The combination of methods is used, biochemical tests, health assessment by specified scales (NIH-NINDS, the Glasgow Coma scale, Rankin scale) and instrumental diagnostics (MRT, CT, EEG, TCCS) amongst them. However, a research into new effective, relatively fast and simple diagnostics methods based on measurements of biological liquids characteristics remains relevant. One of these new diagnostics techniques is a thermoimpedancemetry, which involves an analysis of the temperature dependence of the liquor polarization response to the MHz electric field.

Materials and Methods

We studied the temperature dependence of the full electrical impedance of the measuring cell containing liquids using the set (fig.1) developed at the Ioffe Physical-Technical Institute [1].

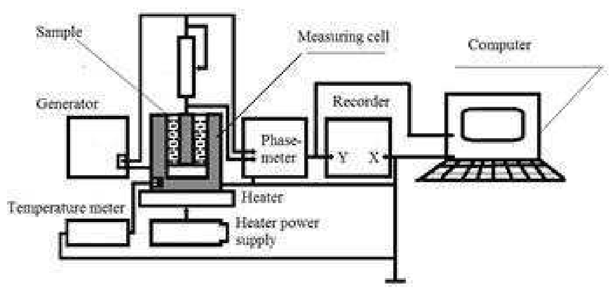

Figure 1: A set for measuring the electrical impedance of liquids

The measuring set characteristics are: operation frequency is 3 MHz, the voltage applied to the measuring cell is 800 mV, temperature range is from 20 to 100°C, the measuring cell type is cylindrical capacitor with the gap between electrode surfaces of 1 mm, height of 20 mm, diameter of 15 mm, the required volume of studied liquid is 1.2 ml, the heating is linear with the rate of 0.026°C/s.

It is well known that electrical impedance is an averaged response of a sample to alternatiing voltage/current and includes active resistance, capacitive and inductive reactance. Our measurements have shown that the electrical impedance temperature dependence for the cell with liquor demonstrates peculiarities whereas the active resistance temperature dependence does not possess any special features, and inductive reactance for the liquids is negligible. The phase measuring method has been applied as the temperature changes of the cell capacitance are very small. It is more useful and precise to measure the phase shift between the applied voltage and the voltage on the measuring cell. This shift is related to the capacity and full impedance by well-known equations. The phase shift discussed is very small and varies from 0.3 to 0.5 degrees of phase. To measure such a small phase shifts a non-standard phase meter with extremely high precision is necessary. In addition, the relation between phase shift and full impedance is rather complicated, and the direct measurements of impedance do not reflect the weak temperature changes of the phase shift.

Results

After measurements, the resulting thermoimpedance curves have been digitized, smoothened and analyzed. The thermoimpedance curves of liquor of more than 300 patients with traumas, insults, cancer have been processed and the high diagnostics value of both the curve shape and the curve parameters have been demonstrated. Firstly, the main parameters of the experimental curves are the temperatures of peaks, the relative intensity and width of these peaks as well as the positions, intensities and half-widths of the components of the decomposition of the experimental curve into the set of Gaussian curves (fig.2). Scaling of axes is not given in fig.2 as it is an example of a thermoimpedance curve, and the exact values of temperatures and capacitance differ from sample to sample. However, the positions of Gaussians peaks which give the best fitting of experimental curves, are in the same relatively narrow temperature intervals for all samples of liquor.

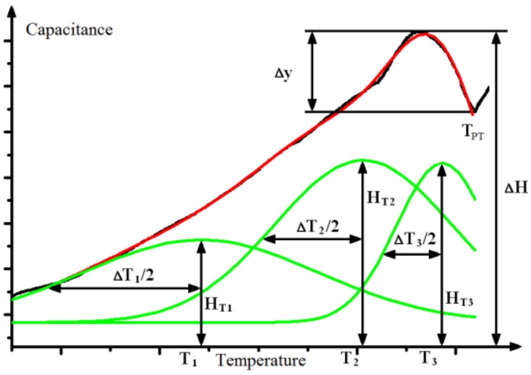

Figure 2: The thermoimpedance curves parameters. The decomposition of an experimental curve (red) into Gaussians (green) is shown.

On the next step, the correlation coefficients between the curve parameters and the biochemical indicators of liquor have been determined. That allowed us to find the distinctive features of the curves matching diseases and to use them for the diagnostics. The separate analysis of curves for the patients suffering from cancer of varying severity has been carried out and the average values of parameters for low and high severity of cancer have been obtained.

The statistical data processing has been made on the hypothesis that the thermoimpedance curve parameters and the liquor biochemical parameters are dependent random quantities. Their relation is determined by the linear regression equation, and its beta coefficient is the correlation coefficient. For each sample (a group of patients) Student inverse distribution has been calculated depending on the number of patients and the confidence level α.

The confidence level corresponded to the value accepted in medical practice (not more than 0.2), and the probability belief value is $p=1-\alpha$. Taking the probability belief not less than 80%, the assurance of the correlation coefficients obtained has been estimated for each group of patients. Using the inverse distribution the interval of correlation coefficients values in which they are statistically significant, has been determined. The certain values of correlation coefficients between the thermoimpedancemetry parameters and biochemical indicators of cerebrospinal fluid have been determined.

Additionally, frequently observed λ-shaped parts of curves (fig.3) have been analyzed in terms of the phase transitions theory and it was shown that at some temperature first-order phase transition occurs in structural elements of liquor.

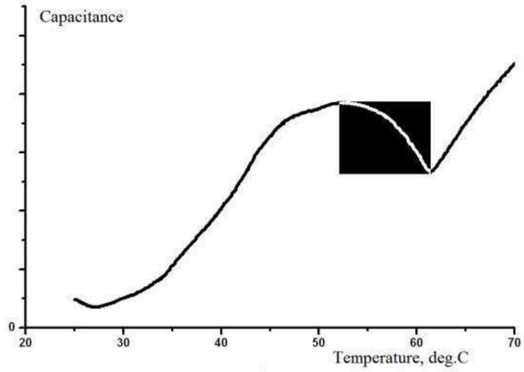

Figure 3: Highlighting of the curve part for the analysis in terms of the phase transitions theory. The typical shape of a curve is given to show the idea.

Discussion

The temperature and relative intensity of the curve peculiarities in the region of the phase transition as well as the critical indexes determined in terms of the phase transitions theory correlate steadily to the protein content in liquor. This means that the basis of thermal changes of the liquor impedance is thermal variation of protein polarizability. Model experiments with protein solutions confirmed that the specific curve shape is mainly due to thermoactivated transitions in proteins ending up with the phase transition “globule-coil”. Our latest experiments with the human serum albumin solutions have demonstrated the 2-stage nature of these transitions.

It is well-known that the phase transition “globule-coil” in proteins is related to denaturation and is an abrupt change of protein conformation due to the thermal destruction of bonds stabilizing this conformation [2]. Proteins are able to perform their biological functions only being in the determined conformations and the disturbing of the conformation leads to the loss of biological activity, which, in turn, can cause some serious diseases called conformation diseases. They are Alzheimer’s disease, Huntington’s chorea, Parkinson’s disease, etc. [3] the search for the diagnostics and treatment methods of which is carried out in the world at present. Also great attention is paid to the study of the liquor proteins state in case of brain ischemia and hemorrhagic disease [4–6]. The possibility of observation of the proteins state and conformation changes enhances significantly the diagnostic value of thermoinpedancemetry and allows us to study physical-chemical background of cerebrospinal diseases.

The thermoimpedance curves of liquor for patients with severe craniocerebral injuries and intracerebral hemorrhage look usually very non-typically. They have been processed using Fourier analysis (data not shown).

The phase spectra of typical and non-typical curves demonstrate well-marked difference, whereas the amplitude spectra differ slightly. Moreover, the Fourier component parameters and the erythrocytes content in liquor correlate strongly.

We suggested that the deviation of the temperature dependence of the liquor polarizability from the standard one is caused mainly by the interaction of protein, mostly albumin, globules with erythrocytes or erythrocyte aggregates [7]. Erythrocytes are cells with non-saturated chemical bonds on their surface [8] and are formed by the ordered network of hemoglobin molecules [9], each of these molecules possessing magnetic moment [10]. As a result, the erythrocytes gain macroscopic magnetic moments [11] which lead to the formation of rouleaus and toroidal-shaped aggregates with surface charge and magnetic moments [8]. These erythrocyte aggregates are several tens of microns in size and are able to form non-covalent bonds with albumin globules which are 5 nm in diameter. Many elements can be observed in liquor, i.e. protein globules and their aggregates, free and protein-bonded erythrocytes, erythrocyte aggregates and their fragments. Consequent thermal destruction of aggregates and the change of transition temperatures of erythrocyte-bonded proteins lead probably to numerous steps of polarizability and the complicated shape of thermoimpedance curves for the samples of liquor containing blood. In addition, the erythrocyte suspension also demonstrates steps of polarizability which can be used for the blood pathology diagnostics [12].

It is to be noticed that the diagnostics and forecasts using the thermoimpedancemetry of cerebrospinal fluid is carried out in Almazov National Medical Research Centre and Prof. Polenov Russian Research Neuro-surgical Institute and in a number of cases has shown its effectiveness.

Conclusions

The cerebrospinal fluid thermoimpedancemetry has been developed and tried out to be a new method for diagnostics and treatment of central neural system diseases.

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