The EIS is a programmable electro medical system (PEMS) including:

- USB plug and play hardware devices including interface box , disposable electrodes, reusable plates and reusable cables
- Software installed on a computer.

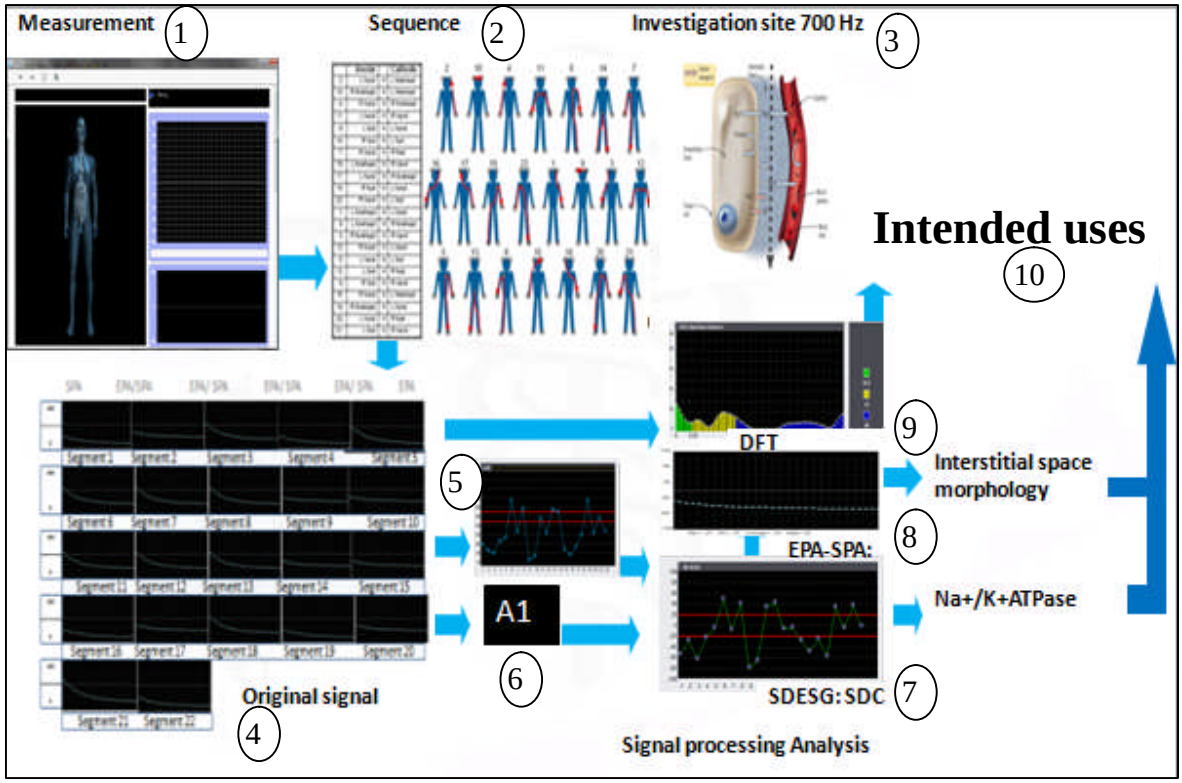
The EIS (Electro Interstitial Scan) provides a signal corresponding to the status of a patient's physiological parameters.

The signal processing analysis displays the following parameters of the living tissue:

- SDC and ESG HF, ESG LF and ESG VLF , according to the Electrical conductivity analysis
- EPA –SPA according to the Electrical dispersion analysis

The device is using the Bioimpedance technology in bipolar mode with a very low frequency.

I. EIS Signal processing Analysis Diagram



Comments of the EIS Signal processing Analysis

1. Measurement of 22 segments of the human body in bipolar mode
2. Sequence of measurement
3. Site of investigation according to the used frequency of 700 Hz: extracellular space.
4. Original signal transmitted to the software
5. ESG graph: real conductivity of the 22 measured segments
6. Calculation of the value A1 (mathematical average of the 22 segments' value)
7. Second derivative ESG from the ESG graph and value A1 and calculation of the parameter SDC related to electrical conductance and the segmental interstitial fluid sodium concentration and segmental ATP pump activity.
8. Dynamic processing analysis and calculation of the parameter EPA-SPA related the electrical distribution and to the parameter alpha of the Cole equation. This parameter is related to the interstitial fluid space morphology.
9. Spectral analysis of the original signal (Discrete Fourier transformation) and calculation of the parameter ESG HF,ESG BHF, ESG LF and ESG VLF. ESG BHF is related to the general interstitial fluid sodium concentration and general ATP pump activity.
10. Cross Analysis of the segmental parameters SDC, EPA-SPA and general parameters HF/LF and VLF for EIS intended use according to the clinical investigations and tissue damage evaluation..

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II. EIS process analysis description

A weak current with a very low frequency (700 Hz) is applied between six electrodes placed symmetrically on the forehead, hands, and feet of the study subject. Each electrode is alternatively cathode and anode (bipolar mode), which permits the electrical conductivity and the electrical dispersion records of 22 segments from the human body (Law of Ohm and α parameter of the Cole equation [(1) (2) (3) (4)]).

Measurement sequence according to the Figure 1

12 segments are related to the body (5/6/7/8/11/12/13/14/19/20/21/22)

10 segments are related to the brain (1/2/3/4/9/10/15/16/17/18).

	Anode		Cathode
2.	L hand	→	L forehead
10.	R forehead	→	L forehead
4.	R hand	→	R forehead
11.	L hand	→	R hand
6.	L foot	→	L hand
14.	R foot	→	L foot
7.	R hand	→	R foot
16.	L forehead	→	R hand
17.	L hand	→	R forehead
19.	R foot	→	L hand
22.	R hand	→	L foot
1.	L forehead	→	L hand
9.	L forehead	→	R forehead
3.	R forehead	→	R hand
12.	R hand	→	L hand
5.	L hand	→	L foot
13.	L foot	→	R foot
8.	R foot	→	R hand
15.	R hand	→	L forehead
18.	R forehead	→	L hand
20.	L hand	→	R foot
21.	L foot	→	R hand

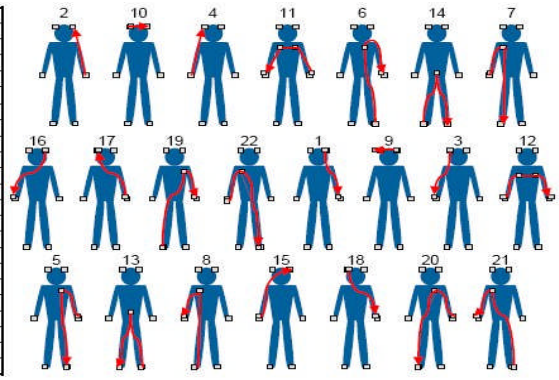


Figure 1

1. Real time Signal

Each segment is measuring during one second, 32 times (resolution of 30 ms). Therefore, the total data is 704 pulses per measurement (Figure 2).

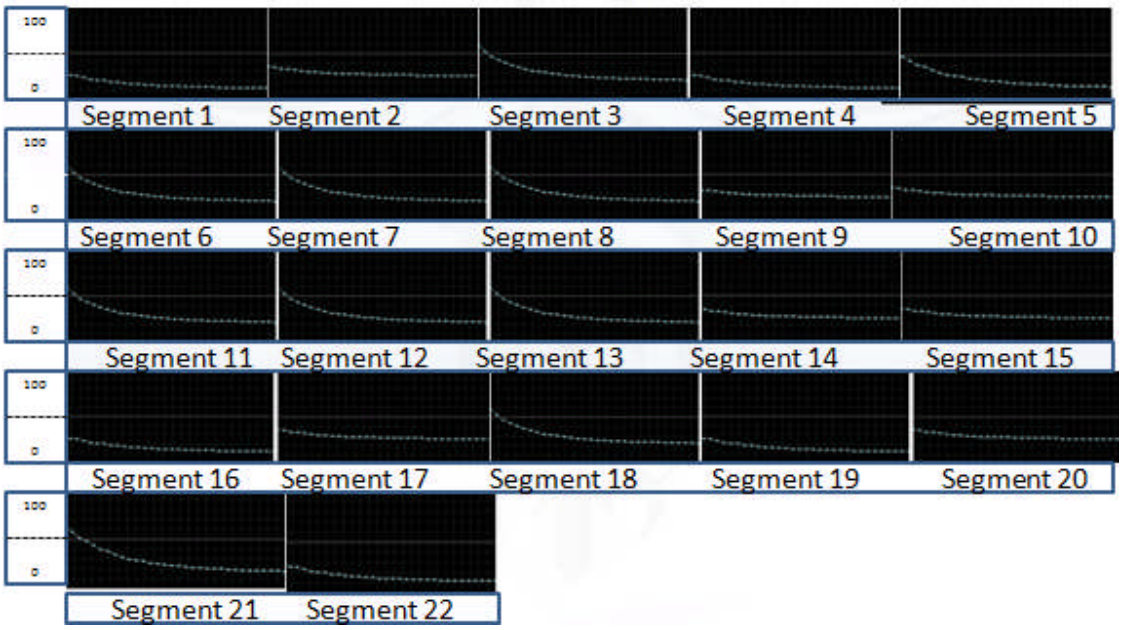


Figure 2

2. ESG graph

The measured parameters are transmitted with a numeric form for each segment, to an informative program.

The electrical conductivity values of the 22 segments are incorporated in a Graph. The graph is called an Electro Scan Gram (E.S.G) (Figure 3).

The abscissa is corresponding to the electrical conductivity in numeric form in scale 0-100 (Conversion table in software features in m.S-1 figure 4)

The ordinate is corresponding to the 22 measured segments of the human body

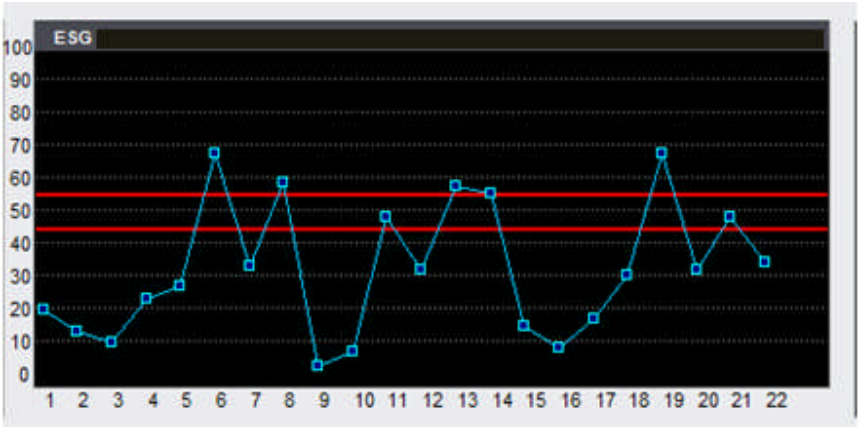


Figure 3

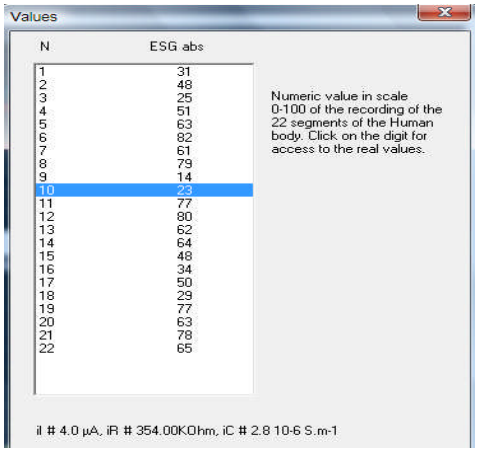


Figure 4

Signal processing analysis:

a. Second Derivative ESG (SDESG)

The ESG is converting to the SDESG graph (Fig.5).

The average of the 22 electrical conductivity values named point A, will be considered as point 0 and therefore the ESG graphic can be convert to second derivative ESG in scale -100/+100. The delta of the numeric value of each segment to the value 0 is called SDC (Standard Deviation of the Conductivity) and can be positive or negative.

The abscissa is corresponding to the conductivity in numeric values with a scale -100/+100.

The ordinate is corresponding to the 22 measured segments of the human body

SDC positive value

SDC negative value

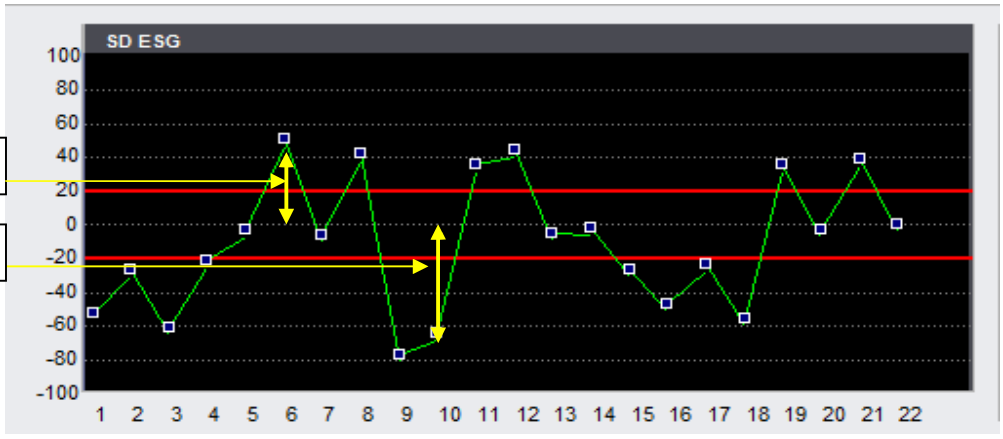


Figure 5

b. Electrical dispersion and Dynamic process analysis

Each segment value is measured with 32 pulses.
The value EPA (End Point Analysis) – SPA (Start Point Analysis) represents the dynamic process value of the signal and the electrical dispersion (closely related to α parameter of the Cole equation). (Fig.6)

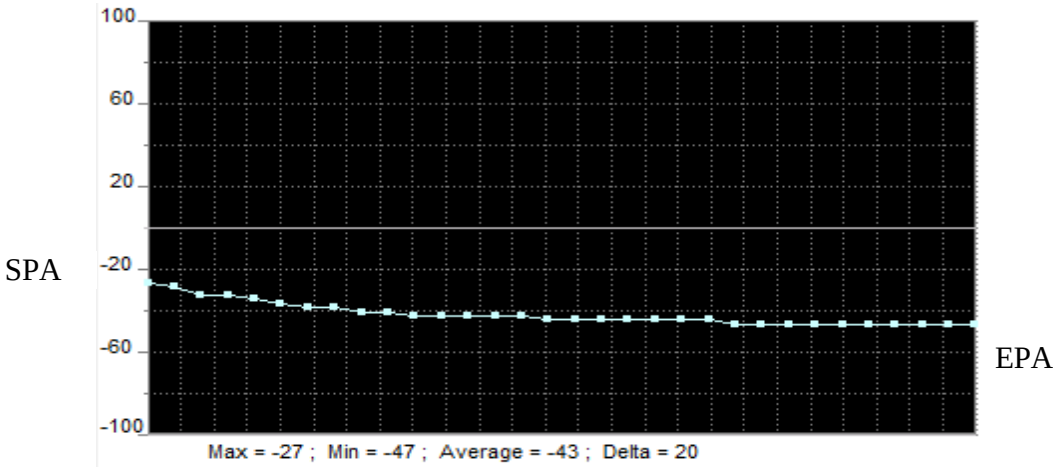


Figure 6

c. Discrete Fourier transform (DFT)

The Spectrum analysis and the Application of the Discrete Fast Fourier Transform [(3)] to the 22 ESG segments and to the body ESG segments provide 4 components where:

- ESG HF (High frequencies from 0.1875 to 0.50Hz), are corresponding to the percent of the high conductivities of the 22 ESG segments.
- ESG BHF (High frequencies from 0.1875 to 0.50Hz), are corresponding to the percent of the high conductivities of the body ESG segments (5 /6 /7 /8/ 11 /12 /13 /14 19 /20 /21 /22).
- ESG LF (Low frequencies from 0.05 to 0.1875 Hz), are corresponding to the percent of the low conductivities of the 22 ESG segments.
- ESG VLF (Very Low frequencies from 0 to 0.05 Hz), are corresponding to the percentage of the very low conductivities of the 22 ESG segments.

ESG HF/VLF ratio is corresponding to the high conductivities / very low conductivities ratio. (Fig.7)

The abscissa is corresponding to the DFT amplitude with a scale 0/100

The ordinate is corresponding to range of frequencies used in DFT (from 0 to 0.50Hz).

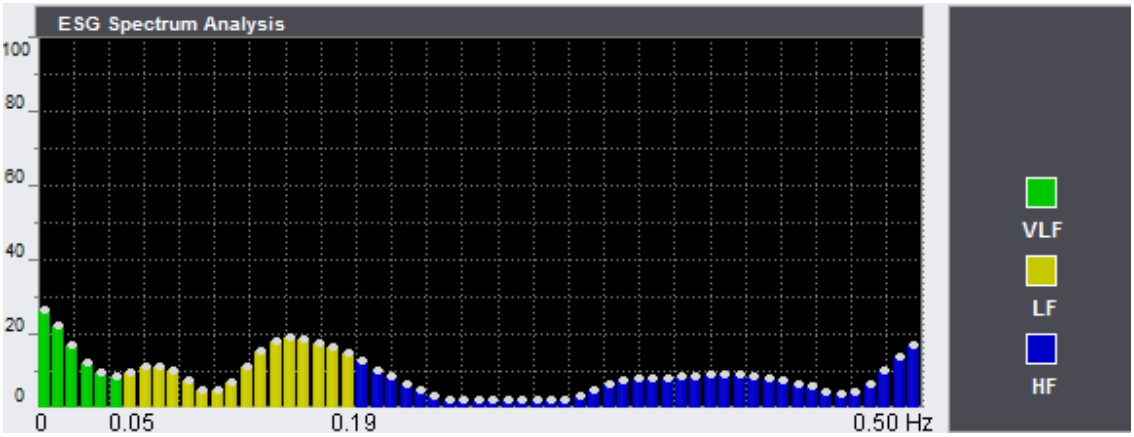


Figure 7

III. Summary of the peer reviews about the Bioimpedance technology and application to the EIS Technology.

1. Electrical Conductance of Living Tissue

a. At low frequencies, near DC, the cell membrane acts as an insulator and the current is not able to penetrate the cell, and most of the current flows around the cell. [12]

b. Considering the extremely low conductivity of the cell membrane, the value of the resistance R of the cell membrane is very high. [1] [12]

c. We can consider living tissue electrically and macroscopically as an ionic conductor. The total ionic conductivity of a solution depends on the concentration, activity, charge and mobility of all free ions in the solution. Ionic conductance is a transfer of charges accompanied by movement of a substance, producing changes in the bulk of the electrolyte. [11] [27]

2. Efflux of the Na+ and ATP production

The ATP production is engaged by the efflux of 3 Na+ ions and the influx of 2 K+ ions. [13]

Application to the EIS Technology (items 1 and 2)

The EIS Technology is using a very low frequency close to the DC, therefore:

a. The current flows around the cells very close to the cell membrane in the area of the interstitial fluid and does not penetrate the cell
b. The EIS measurements are in KOhms and the normal range average of the measured resistance is high, about 100 KOhms and the conductivity around 24 10-6 S.m-1.
c. The segmental and general percent of high conductivities are proportional to the interstitial fluid Na+ ions concentration (segmental parameter SDC and general parameter

ESG BHF) and according to the Na+/ K+ ATPase pump principle; the conductivity is proportional to the mitochondrial ATP production.

3. Electrical Dispersion and dielectric properties

Any material with the ability to store capacitive energy can be classified as a dielectric.
The cell membrane is the cellular structure has the main contribution to the dielectric behavior of living tissue. (5) (10)
Living tissue is considered as a dispersive medium (10): In the case of living tissues, the spectral width of the electrical Bioimpedance dispersions (related with α parameter in the Cole equation) is related with the morphology of the extracellular spaces. (20)

Application to the EIS Technology (items 3)

The electrical Bioimpedance dispersion (parameter EPA-SPA of the ESG table closely related with α parameter in the Cole equation) is related with the morphology of the extra-cellular spaces.

4. Electrode polarization impedance

The contact area of the electrodes with electrolyte is playing a role on the electrode polarization impedance, as the electrode polarization impedance is inversely proportional with electrode surface area. [21]

Application to the EIS Technology (item 4).

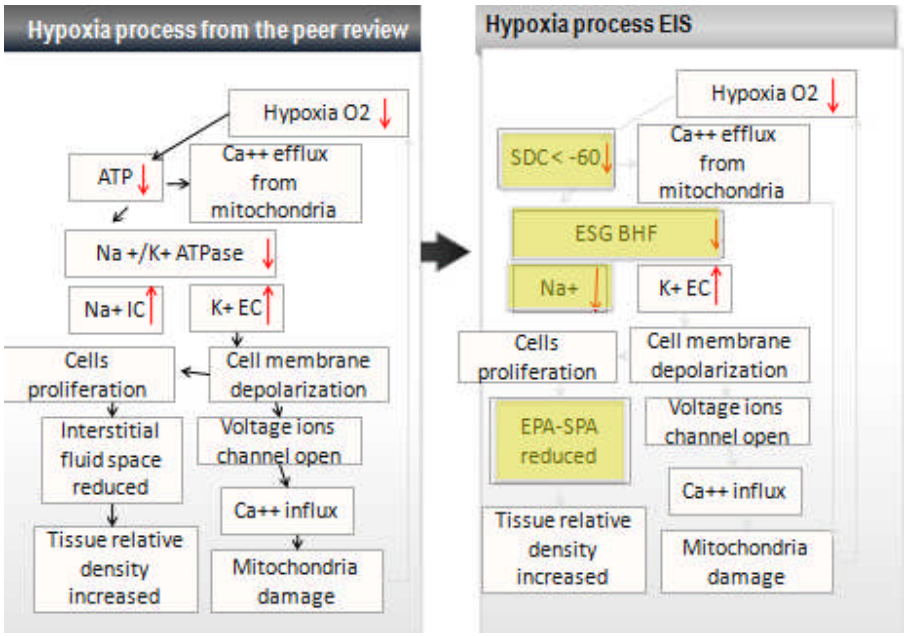
a. As regard to the used big size and planar electrodes, the electrode polarization is very low.

V. Cellular Damage and Bio impedance.

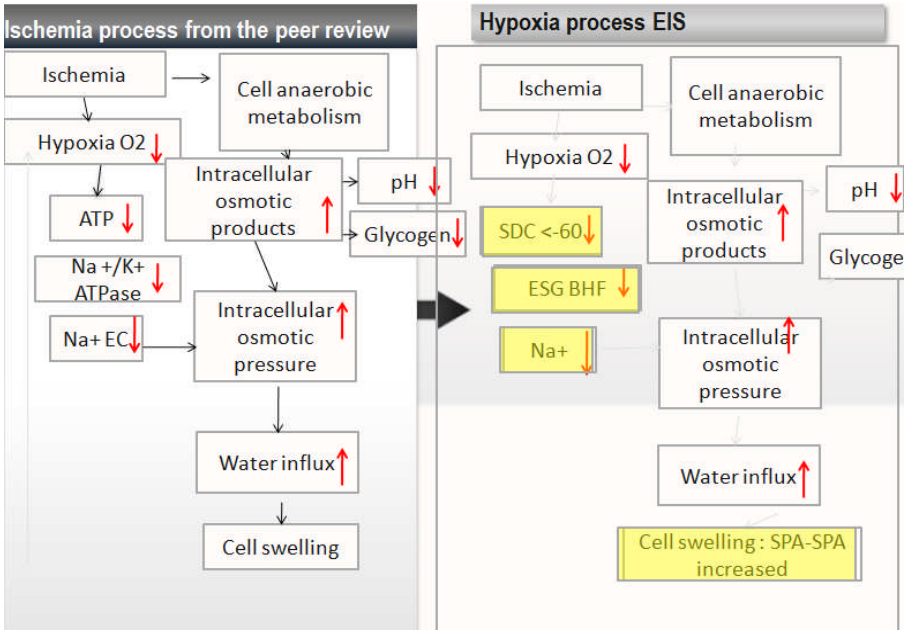
Introduction to Cellular Damage [22] [23]

The cell is usually confined to a narrow range of functions. This function specificity of the cell is due partly to its genetic program and partly to the surrounding environment, the availability of energy sources and the capacity of its metabolic pathways. The state of the cell when it is able to handle normal physiological demands is denominated homeostatic steady state.
In the presence of a pathological stimulus or excessive physiologic stress, the cell has the capacity to adapt itself, achieving a new but altered steady state to preserve the viability of the cell. This process is denominated cellular adaptation, and when the limits of the adaptability of the cell are overcome, cell injury occurs.
Depending on the severity and the duration of the stimuli, cell injury is reversible up to a certain point – after which irreversible cell injury occurs, leading to cell death. The capacity of the cellular adaptation varies among different type of tissues, and brain tissue exhibits a very high sensitivity to hypoxic insults (A. C. Guyton & J. E. Hall 2001, T. Acker & H. Acker 2004, V. Kumar 2005)*.

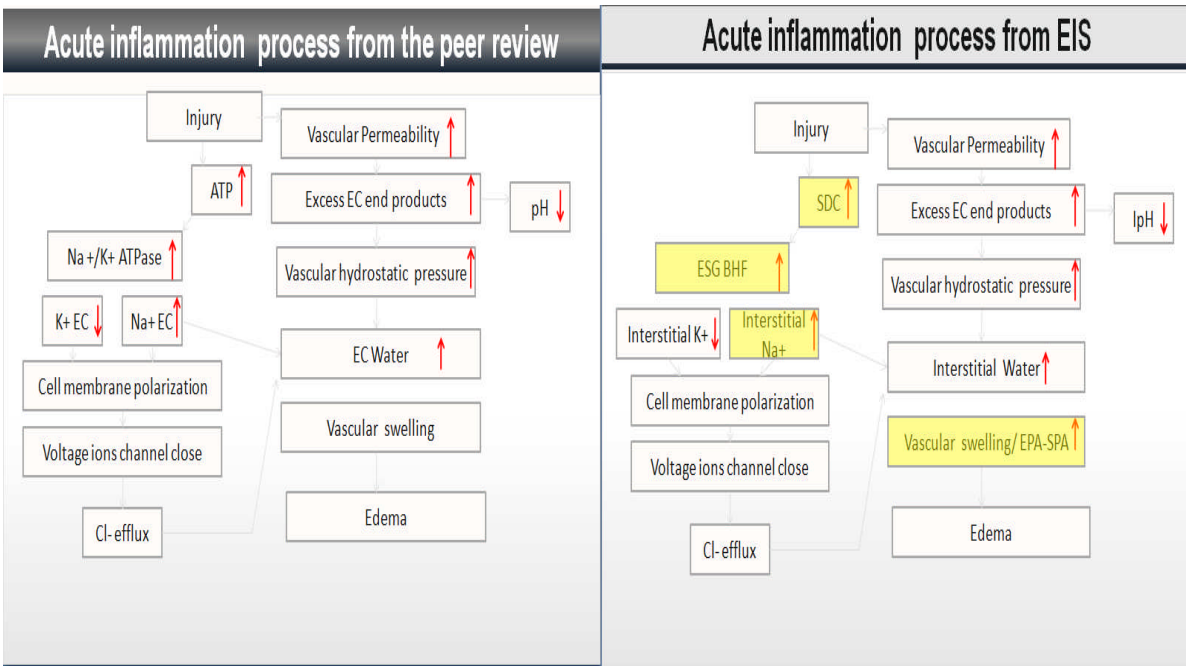
1. Hypoxia and cells proliferation process of the living tissue



2. Ischemia process of the living tissue

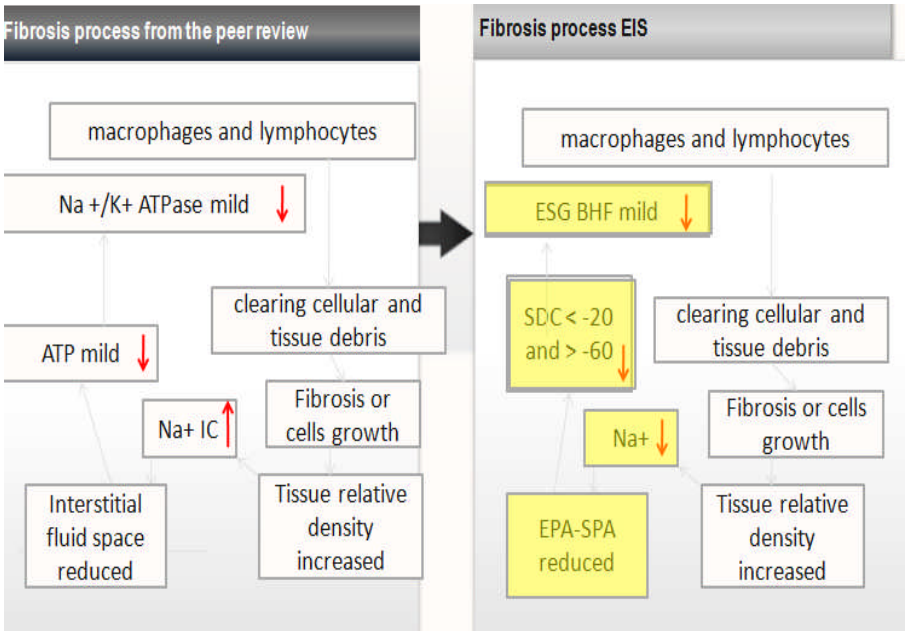


3. Acute inflammation process of the living tissue

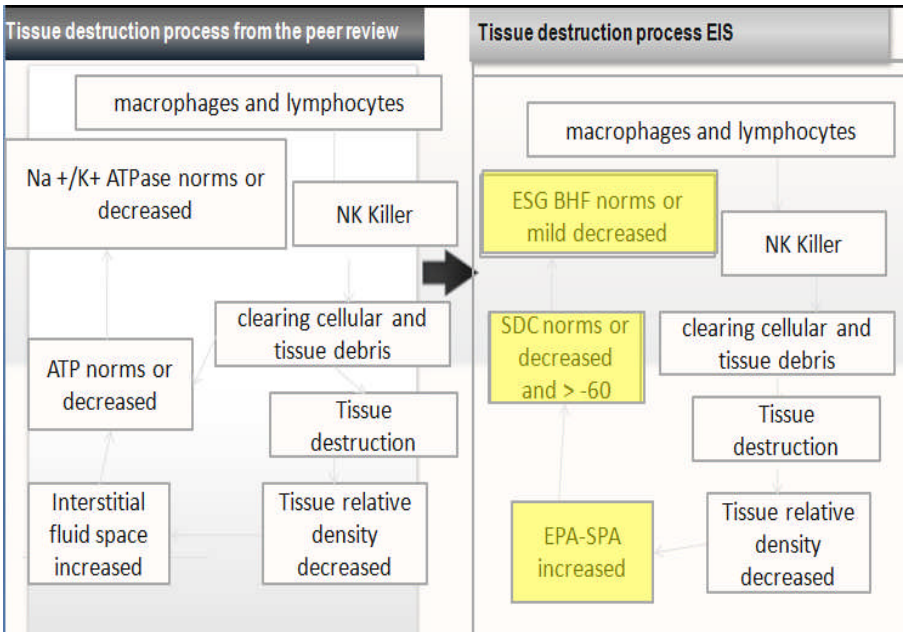


4. Chronic inflammatory process of the living tissue ([13])

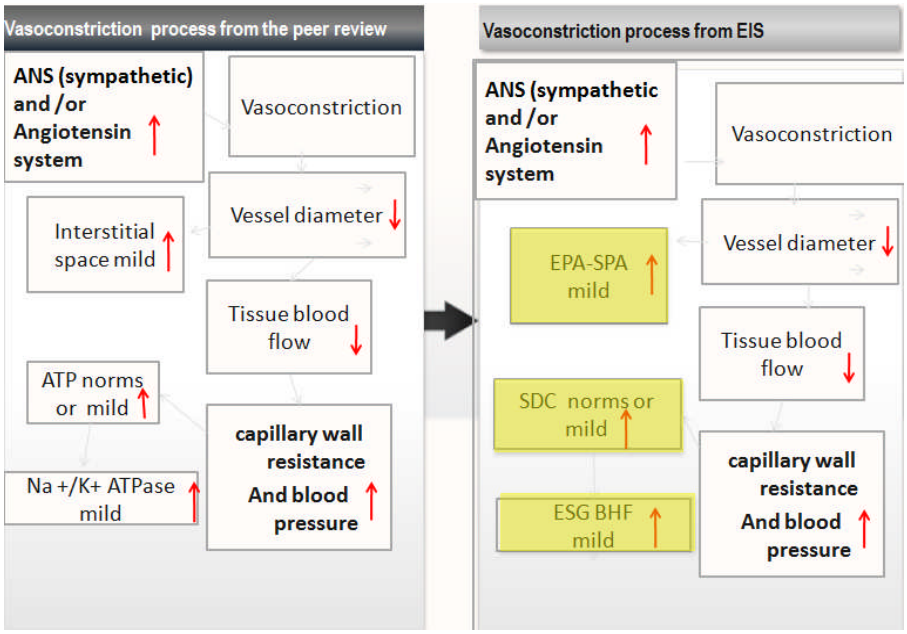
4.1 Chronic inflammation with fibrosis or cells growth



4.2 Chronic inflammation with tissue destruction

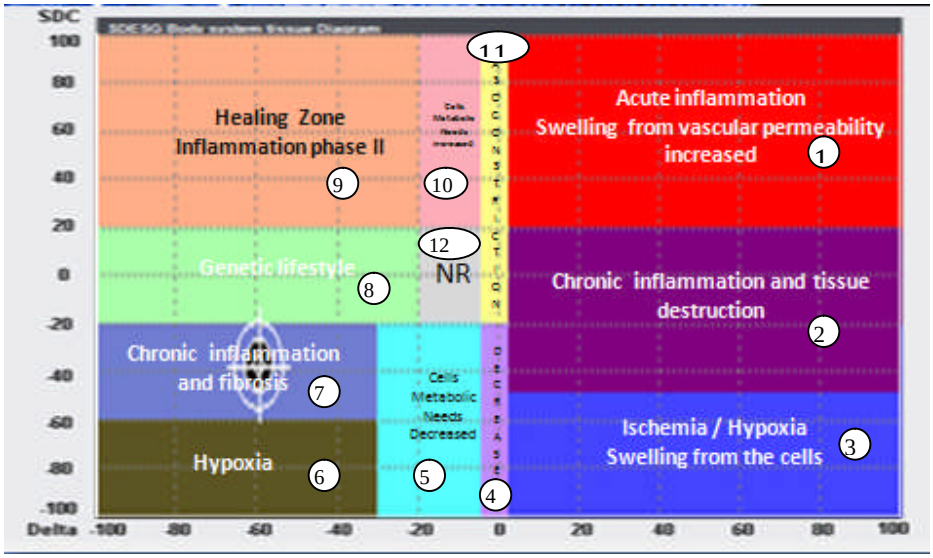


5. Vasoconstriction ([13])



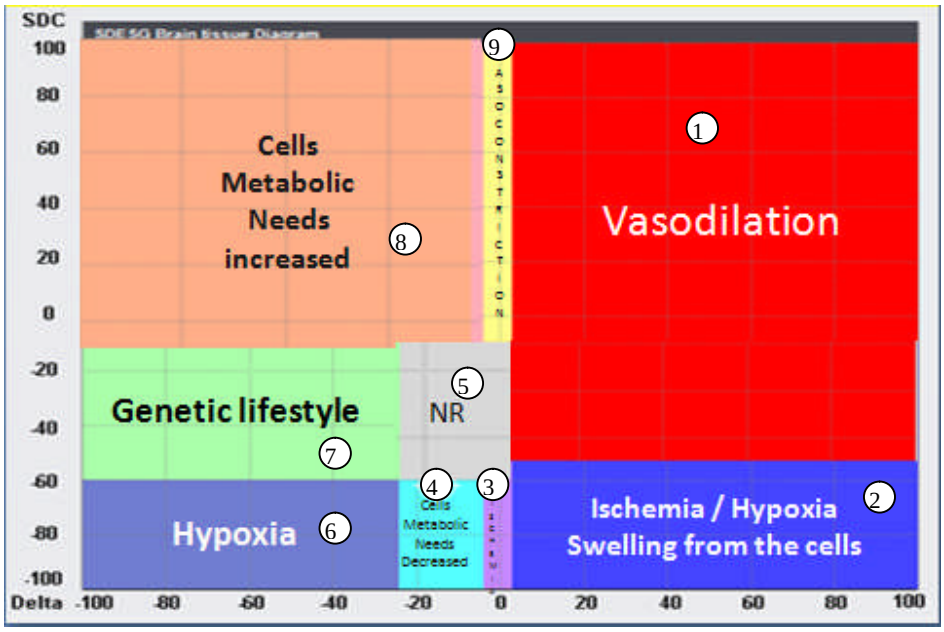
Segmental zone localization:
According to the mathematical calculation of the Venn diagram
Segments 1/2/3/4/9/10/15/16/17/18 are corresponding to the brain living tissue.
Segments 5/6/7/8/19/20/21/22 are corresponding to the digestive system living tissue.
Segments 11/12 are corresponding to the thyroid living tissue.
Segments 13/14 are corresponding to the genitourinary system living tissue.

Interpretation of the results
ESG body diagram



Color coded Diagram ESG: ATP production, (SDC) in abscissa, and interstitial space morphology, (EPA- SPA) in ordinate.
Zone 1: ATP increased, and vascular swelling: Acute inflammation
Zone 2: ATP normal range, and vascular swelling: Chronic inflammation, and tissue destruction
Zone 3: ATP decreased, cells swelling: ischemia and hypoxia
Zone 4: Pre ischemia, function decreased.
Zone 5: ATP decreased, EPA- SPA normal range: cells metabolic needs decreased, genetic or lifestyle.
Zone 6: ATP decreased, and EPA- SPA decreased: hypoxia, cells growth and tissue proliferation.
Zone 7: ATP mild decreased, and EPA- SPA decreased: chronic inflammation, with fibrosis or scar
Zone 8: ATP normal range, EPA- SPA decreased: zone or inter individual variation, genetic or lifestyle
Zone 9: ATP increased, and EPA- SPA decreased: Healing zone
Zone 10: ATP increased, and EPA- SPA normal range: cells metabolic needs increased, stress or high blood pressure
Zone 10: ATP normal or Increased, interstitial space mild increased, and no swelling: zone of vasoconstriction
Zone 11: Vasoconstriction
Zone 12 : Normal range

Interpretation of the ESG brain Diagram



1. Vasodilation:
2. Ischemia/hypoxia :
3. Pre ischemia:
4. Cells metabolic needs decreased :
5. Normal range
6. Hypoxia: serotonin decreased,
7. Genetic. lifestyle
8. Cells metabolic needs increased:
9. Vasoconstriction:

Interpretation of the Spectral analysis

ESG HF: Proportional to the sympathetic system activity (36)
ESG BHF: Proportional to the general interstitial fluid Na+ concentration and general ATP production.
ESG HF/VLF: proportional to the blood viscosity.
ESG LF and VLF: no interpretation.

IV. Validation of the parameter SDC and EPA-SPA:

SDC parameter evidence bases

1 Clinical investigation Botkin 2006 [34]

Thyroid treatment monitoring

The findings show that SDC and TSH has a significant negative correlation to each other (r = -0.975, p = 0.005). It shows that, SDC shares approximately 95.1% (that is (-0.975)2x100% or 0.951x100%) of its variability with TSH.

2. Clinical Investigation in University of Miami Miller School of Medicine, Miami, FL 33136 USA 2010 [35]

The correlation between the EIS spectrum analysis and HRV variables was also very high (r=.76, p < 0.001), suggesting that the high conductivity ratio has predictive capability on the sympathetic nervous system activity.

3. Conclusion:

In the above investigations we found a high correlation between:

- The Thyroid activity (TSH) and SDC.
- The sympathetic system activity (HRV) and SDC spectrum analysis.

The thyroid activity and the sympathetic system activity are known parameters to increased the cells exchanges [13]

EPA-SPA parameter evidence bases

1 Clinical investigation Botkin 2006 [34]

1.1 Follow-up of patients using anticoagulants:

The findings show that EPA-SPA 6/13/19 and PI (Prothrombin Index) has a significant positive correlation to each other (r = 0.961, p = 0.009). It shows that, PI shares approximately 92.4% (that is $(0.961)^2$x100% or 0.924x100%) of its variability with EPA-SPA 6/13/19. Thus, a high value of EPA-SPA 6/13/19 corresponds to high values of PI or low value of EPA-SPA 6/13/19 corresponds to low values of PI.

1.2. SSRI treatment monitoring.

The findings indicate that there were a significant positive correlations between EPA-SPA and the treatment Response at D+45 (rho = 0.709, p < 0.001) and D+60 (rho= 0.804, p < 0.001).

2. Conclusion:

The clinical investigation had shown the following items:

- The parameter EPA-SPA decreased with the PI.
- The parameter EPA-SPA increased with the cerebral serotonin level

The PI is related to the ischemia risk and the fact that the parameter EPA-SPA decreased with the PI level is showing that the EPA-SPA increased is an indicator of the ischemia risk. **(13)**

The Depression is related to the cerebral tissue hypoxia and the fact that the parameter EPA-SPA increased with the treatment response is showing that the EPA-SPA decreased is an indicator of the hypoxia. [13]
These facts are corresponding to the peer reviews related to the parameter α of the Cole equation [20], and the parameter EPA-SPA is independent of the impedance measurement (SDC parameter). [20]

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