Monitoring EIS System versus Monitoring Conventional diagnosis

Clinical Test Reference No. 1490030664789

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Ethics Committee Agreement
May 19, 2006

Site of Investigation
Department of Physiology
S. P. Botkin Clinic and Hospital

Final Report / Per Protocol of Clinical Investigation (P.I.C.) Reference No. TC 02
September 15, 2006
Clinical investigations were conducted at the S.P. Botkin Hospital from May 20, 2006, to September 1, 2006, in order to evaluate the clinical application of the Electro Interstitial Scan (E.I.S), we performed drug administration studies.

Two hundred fifteen (215) test subjects (Age $54 \pm 16$) were recorded with the EIS System. These patients presented affections diagnosed by supplementary and conventional examinations (hypothyroidism, hypertension, atherosclerosis or thrombosis risk, and Major depression) and were undergoing no treatment.

The recruitment criteria had been agreed upon before the tests began. The treatments corresponding to the diseases were decided by the conventional examinations results, and a follow-up being undertaken on one hand with the EIS System and on the other hand by conventional methods.

Hypotheses tested:
The EIS can be used for the monitoring treatment?
The hypothesis was validated.
The EIS system seems accurate for the monitoring of the drugs’ monitoring of the considered diseases:

- **Hypothyroidism:**
  Monitoring of the EIS system versus laboratory test (TSH) with the thyroid substitute treatment $r^2 = 0.79 \ P < 0.0001$

- **High blood pressure:**
  Monitoring of the EIS system versus NIBP measurement with the Beta blockers treatment $r^2 = 0.78 \ P < 0.0001$
  Monitoring of the EIS system versus NIBP measurement with CEI treatment $r^2 = 0.78 \ P < 0.0001$

- **Atherosclerosis and/or thrombosis risk:**
  Monitoring of the EIS system versus laboratory test (Prothrombin Time) with the anticoagulant treatment $r^2 = 0.91 \ P < 0.0001$

- **Major depression:**
  Monitoring of the EIS system versus the depression’s symptomatology with the SSRIs treatment $r^2 = 0.87 \ P < 0.0001$
Pre-study summary
Pre studies had been run in France in Gustave Roussy (2001) Institute and St Louis Hospital (2003) for provide a normal range of the ESG graph and respectively changes in ESG graph for the patient with pains after chemotherapy treatments and patients with erectile dysfunction (ED). In 2004, clinical trials run at the Botkin Hospital with the EIS system on 589 patients presenting a panel of 20 groups of subjects (one group of healthy subjects and 19 groups of subjects presenting varying pathologies diagnosed by conventional methods) enabled the system to acquire new algorithms of segments ‘values of ESG graph and corresponding organs.

FOREWORD
The pre studies and the clinical investigation had done at the Botkin Hospital in 2004 were only made for improve, determinate the normal range of conductivity of the ESG graph and adjust the algorithms in the EIS system, but do not give any information about the EIS intended uses. The questions that remained were what about its claims and intended use?

Material and Methods
Technical data
The EIS System, linked to a computer, constitutes a programmable electro-medical system (PEMS) in the sense of the standard EN60601-1-4. It includes electronic hardware and software installed on a computer, and a USB cable linking the computer and the electronic box. It is recommended that the computer be placed outside the patient’s immediate environment and be certified to comply with IEC 60950-1.

Technical Data of the Device

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power supply</td>
<td>5V (power supply by USB port)</td>
</tr>
<tr>
<td>Power supply frequency (Hz)</td>
<td>Direct current</td>
</tr>
<tr>
<td>Power consumption</td>
<td>200mA</td>
</tr>
<tr>
<td>Classification</td>
<td>Class II</td>
</tr>
<tr>
<td>Degree of protection against electric shocks</td>
<td>BF</td>
</tr>
<tr>
<td>Operating mode</td>
<td>continuous</td>
</tr>
<tr>
<td>Tension on the electrodes, in operating mode</td>
<td>1.28V</td>
</tr>
<tr>
<td>Dimensions in mm</td>
<td>128 X 143 X 33</td>
</tr>
<tr>
<td>Weight</td>
<td>1.2 kg</td>
</tr>
</tbody>
</table>

Accessories

<table>
<thead>
<tr>
<th>Component</th>
<th>Technical specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disposable forehead electrodes</td>
<td>Ag/AgCl @ 15.75 cm²</td>
</tr>
<tr>
<td>2 reusable hand electrodes</td>
<td>Polished stainless steel 272 cm²</td>
</tr>
<tr>
<td>2 reusable feet electrodes</td>
<td>Polished stainless steel 330 cm²</td>
</tr>
<tr>
<td>3 audio-type cables to connect electrodes to the electronic controller box</td>
<td>2-m-long armored insulated cables. Color-coded for ease of use.</td>
</tr>
<tr>
<td>USB cable</td>
<td>2-m-long standard USB cable connecting electronic controller box to PC</td>
</tr>
</tbody>
</table>
Contraindications
Persons were excluded from the study who:

- Undergoing external defibrillation
- Had skin lesions in contact with the electrodes or excessive perspiration
- Sinusitis and in particular the frontal sinusitis could change the conductivity of the ESG segments 1/3/9/10/16/18
- Had been fitted with cardiac pacemakers, patients connected to electronic life support devices, or any implanted electronic device.
- Were unable to sit or to not move during 3 minutes (e.g. Parkinson disease)
- Had been fitted with metallic pins or prostheses in digits or joints
- Were pregnant women after the sixth month
- Were missing one or several limbs

Material furnished for the clinical trial
1. Safety of the EIS System: Type EIS-01-USB attestation EN 60601-1-1 and EN 60601-1-2
2. Instructions for use in English and also translated into Russian
3. A system including:
   - An electronic box serial number 03/31/008
   - Three sets of audio cables
   - Electrodes (stainless steel) for hands
   - Electrodes (stainless steel) for feet
   - 1,000 disposables electrodes for the forehead
   - A USB cable
   - A Laptop computer Toshiba Model PSLB0E-01D014RU Number 682186265 certified to comply with IEC 60950-1 with the EIS software installed version 7.81

Measurements:
A direct current of 1.28V 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 recording of 22 segments from the human body (measurement sequence according to the figure 1). The intensity is transmitted with a numeric form (with a scale -100/+100) for each segment to an informative program.
The graph of 22 segments is called an Electro Scan Gram (ESG) (Figure 2). The intensity value is converting to conductivity by application of the Law of Ohm U = RI then C = 1/R, incorporated in the ESG graph. The converting table into intensity/Resistance and conductivity is available on the software.
The statistical normal range of the values of the ESG had been determine from the control groups of the pre-studies in France (Gustave Roussy Institute and St Louis Hospital) and of the clinical investigation Botkin 2004 (Figure 3 and Table 1).

The used techniques are the electrical Bio Impedance Analysis (BIA) and the Bio Impedance Spectrometry (BIS). The BIA is used in many applications like the estimated of the body composition and water balance (5),(14) but also in cardiology (3),(13) and imaging (19). The BIS is used for estimated the body composition and water balance (5),(14), but also for estimated the neurotransmitters (23)(24). The specificity of the examination is the utilization of a voltage of 1.28 V in DC (direct current) that cannot cross the cellular membranes and capillaries (High resistance in KOhms and reactance 0) and therefore can only reach the interstitial fluid (Interstitial tissue), whose intensity, resistance, and conductivity can then be measured.
These facts were confirmed by the research of Kanai and Meijer\(^{(11), (18)}\), i.e., that the cellular membrane and capillaries behave as one capacity because of dielectric properties, so a direct current cannot penetrate its membranes and circulate solely in the interstitial fluid. The tissues constitute an electrolytic environment; conduction of electric current is assured by the ionic porters under the effect of a tension applied between two electrodes.\(^{(14)}\). The conductivity is also related to the volume (water content) of the space traversed\(^{(14)}\) (Interstitial Fluid).

The electric current is sending from anode to cathode and therefore the sodium (higher extracellular concentration in positive charges) represents the main ionic porters. Figure 4 and 5 are showing the correlation of the interstitial fluid intensity and the Na\(^+\) concentration.\(^{(5)}\) The figure 5-1 is showing the correlation between the volume (water content) and the traversed compartment conductivity.\(^{(14)}\).
The normal were calculated by the formula of the TWB and an empirically derived coefficient (Statistic analysis of the above databases) related to the age, height, weight, and the gender of the subject. Formula of the calculation of TWB (total body water) $v = \rho \frac{Ht^2}{R} \Rightarrow R = \frac{\rho v}{Ht^2}$

### Calculation of $\rho$: Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>$\rho$ Men</th>
<th>$\rho$ Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/6/78/910/11/12</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td>13/14/1516/17</td>
<td>1.20</td>
<td>1.20</td>
</tr>
<tr>
<td>18/19/20/21/22</td>
<td>1.15</td>
<td>1.10</td>
</tr>
<tr>
<td>23/24/25/26/27</td>
<td>1.10</td>
<td>1.07</td>
</tr>
<tr>
<td>28/29/30/31/32/33/34/35/36/37</td>
<td>1.07</td>
<td>1.05</td>
</tr>
<tr>
<td>38/39/40/41/42</td>
<td>1.05</td>
<td>1.0</td>
</tr>
<tr>
<td>43/44/45/46/47</td>
<td>1.0</td>
<td>0.98</td>
</tr>
<tr>
<td>48/49/50/51/52</td>
<td>0.98</td>
<td>0.96</td>
</tr>
<tr>
<td>53/54/55/56/57</td>
<td>0.95</td>
<td>0.93</td>
</tr>
<tr>
<td>58/59/60/61/62</td>
<td>0.93</td>
<td>0.91</td>
</tr>
<tr>
<td>63/64/65/66/67</td>
<td>0.91</td>
<td>0.89</td>
</tr>
<tr>
<td>68/69/70/71/72</td>
<td>0.90</td>
<td>0.88</td>
</tr>
<tr>
<td>73/74/75/76/77</td>
<td>0.88</td>
<td>0.86</td>
</tr>
<tr>
<td>78/79/80/81/82</td>
<td>0.85</td>
<td>0.83</td>
</tr>
<tr>
<td>83/84/85/86/87</td>
<td>0.80</td>
<td>0.81</td>
</tr>
<tr>
<td>88 and more</td>
<td>0.78</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Figure 4

Figure 5

Figure 5 -1
By Using the Chronoamperometry \(^{(1)},(2)\), (Cottrell equation), The EIS system allows the calculation of the interstitial fluid ionograms and interstitial fluid H\(^+\) concentration \(^{(21)}(22)\) (Figure 6) according to the ionic flux (ionic Diffusion coefficient) \(^{(12)}(16)\).
Effect of inter capillary distance (interstitial fluid volume) in relation with the tissue oxygen delivery. In case of increased of interstitial volume, the oxygen delivery is reduced \(^{(32)}\). (Figure 7).

![Figure 7](image)

**Precaution for use**

1. Utilization of direct current in human body provokes some side effects as a capacitive effect at the level of each electrode and skin of the order of a few µm corresponding to the effective charge of the field around the electrode (electrochemical deposition) and increased the \(\text{Na}^+/\text{K}^+\) ATPase pump during 15 to 25 minutes \(^{(14)}\).

2. Measurement conditions

   The measurement depend the area of the electrodes, the ambient temperature and the distance of the electrodes.

   To avoid the above side effects:

   Before each measurement, it is necessary to clean the reusable electrode and the skin in contact with the electrode with Cidex for deletes the depositions.

   The reproducibility of the measurements is possible only if the time between the 2 examinations is > 30 minutes. It is not recommended to make more than one measurement each week for the same subject.

   Area of the electrodes: Use only the electrodes supply by the Manufacturer

   Distance of electrodes: The Instruction for use provide the placement of electrodes and the distance to respect between the electrodes

   Ambient temperature: Optimal temperature 20\(^\circ\)-23\(^\circ\)C
JUSTIFICATION OF THE STUDY

Data from the literature
Data were available from the results of bio-electro impedance \(^{(13)}, (14), (19)\), and the clinical investigations from interstitial fluid research \(^{(25)}, (26)\).

Justification of the study considering current knowledge
The physiology of interstitial fluid is still poorly known due to conditions of sampling. The electrical measure in vivo might bring new elements to the level of our internal environment and, similar to blood tests, might be monitoring the treatment of certain pathologies.

Objective of the study
The goal of this study was to evaluate the EIS System in treatment monitoring of specific diseases versus the conventional techniques.

CRITERIA OF PRINCIPAL JUDGMENT

To control the efficacy of treatments administered to cure or attenuate a disease, estimated at the level of administered treatments of the same pathologies in follow-up by conventional examinations and the values of different segments ESG. The ESG values were to be compared to laboratory tests values or to measurement by other medical devices or to the symptomatology (response or no response in Major depression).

The statistical analysis of results was to be undertaken by the program STATISTICA, version 7.0, using the following methods:
- Mean Plot: Whisker: CI: 0.95 %
- Scatter gram

Hypotheses tested
1. The EIS System can be validated in treatment monitoring
2. The EIS System cannot be validated in treatment monitoring

STUDY CONDITIONS

Decision of the Ethics Committee
Following agreement of the Ethics Committee on May 19, 2006, the trials began May 20, 2006, based on the Declaration of Helsinki.

Conformity or modifications to the protocol (I.P.C) of February 25, 2006
- Protocol (Ref. TC 02) was submitted for agreement to the Health Ministry of Russian Federation
- No modification to the device was made during the trial.
- The trial followed in a consistent manner the investigation protocol plan (I.P.C.).
- No side effects were recorded following registration.

Disclosure: Financial interests and arrangements of clinical investigation. The FDA 3455 Form was signed between the sponsor and the clinical investigator.
Certification: Financial interests and arrangements of clinical investigation. The FDA 3454 Form was signed between the sponsor and the clinical investigator.

Confidentiality
- Confidentiality was respected by all involved persons throughout the investigation.
- All data were secured and inaccessible to non-involved persons.
- The confidentiality of information relative to each subject as well as to his or her private life is to be preserved in the records and in all publications of data of the clinical investigation.
- The reports will include a patient code automatically generated by the EIS program giving each patient’s gender, full name, and date of birth.

Duration of the study
Patient registrations were conducted from May 20, 2006, to September 2, 2006.

Total number of patients
The number of patients for this study comprised 103 men and 112 women, age of 54± 16.

Determination of the calculation of the number of patients
The calculation of the number of patients required was based on the databases of the preliminary clinical studies using DC bioelectric impedance at the French hospitals Gustave Roussy Institute (39 subjects, with 40 in the control group) in 2003 and St. Louis Hospital in 2005, and from Russia’s S.P. Botkin Hospital (589 patients comprising 20 groups of about 30 subjects each) in 2004.

Determination of the calculation of the number of patients $P$ for the current study was made according to the following formula:

$$
\alpha = 5\%
$$

Test power of 80% power = $F(\Delta, \ N, \ variability \ DS)$, taking into account the criteria of judgment

Considering the judgment criteria $\Delta$ at approximately 20 DS (5% error), the number of patients $P$ could be equal or $> 20$ by condition ($p < 0.005$). With a research algorithm of four groups, the number $P$ of patients could not be fewer than 80 ($20 \times 4$).

Clinical inclusion criteria
Inclusion was made of patients based on their medical files after diagnosis by conventional means. None was undergoing treatment. Subjects presented one of the following pathologies:
- Hypothyroidism
- Hypertension
- Atherosclerosis
- Major depression

In addition, each patient:
- Had to present one isolated disease
Could not present a contraindication to the EIS System measurement
Had to be between 20 and 75 years of age
Had to sign the enlightened consent form based on the principles of the Declaration of Helsinki

Criteria of non-inclusion.
Patients were excluded from the study who:
- Had a general contraindications for EIS measurement
- Had had treatment such as chemotherapy or deep surgery
- Were not afflicted with the four diseases being studied
- Were in treatment
- Presented an important deviation from the prevalence of the diseases
- Had difficulty in the associated pathologies, e.g., hypertension, atherosclerosis, and diabetes
- Present neurological diseases causing them to be unable to sign the consent form
- Were under treatment
- Could not be included according to the investigator

METHODS OF ANALYSIS OF MEASURED PARAMETERS

Strategy of analyzing the data
According to the pathologies, the analysis of data would be different.

- **Hypothyroidism**: Following prescription of a Thyroid hormone, the values (numeric values in scale -100/+100, noted every 15 days and change of the dose per day) of the conductivity of the segments 11 and 12 of the ESG graph would be compared to the values from the laboratory TSH test (the sampling was performed immediately after the EIS measurement).
- **Hypertension**: Following prescription of a beta-blocker, the values (numeric values in scale -100/+100 noted every 15 days) of the conductivity of the segments 2, 4, 15, and 17 of the ESG would be compared to the values of conventional blood pressure measurement. (the measurement was performed immediately after the EIS measurement)
- Following prescription of a Converting Enzyme Inhibitor of Angiotensin (CEI), the values (numeric values in scale -100/+100 noted every 15 days) of the conductivity of the segments 6, 8, 19, and 21 of the ESG would be compared to the conventional blood pressure measurement (the measurement was performed immediately after the EIS measurement)
- **Atherosclerosis or thrombosis risk**: Following prescription of an anticoagulant treatment, the values (numeric values in scale -100/+100 noted every 3 days) of the conductivity of the segments 6, 13 and 19 of the ESG would be compared to the values (noted every 3 days) from the laboratory Prothrombin time test. (the sampling was performed immediately after the EIS measurement)
• Depression: Following prescription of an SSRI treatment, the values (numeric values in scale -100/+100 noted every 15 days) of the conductivity of the segments 1,3,9,10,16 and 18 would be evaluated based on the symptomatology (response or no response) of the Major depression.

Number of patients in the study groups
• Group 1: Hypothyroidism—52 patients
• Group 2: Hypertension—57 patients
  This group was divided into two subgroups based upon the prescribed treatments:
  - Group 2A (37 patients)
  - Group 2B (20 patients).
• Group 3: Atherosclerosis—49 patients
• Group 4: Depression—57 patients

Treatments provided for the groups of patients
• Group 1: Thyroid treatment
• Group 2A: Beta-blockers
• Group 2B: CEI (Converting Enzyme Inhibitors)
• Group 3: Anticoagulant
• Group 4: SSRI
RESULTS

After beginning treatment, the measurements took place every 15 days (for group 1, 2A, 2B and 4) and every 3 days (for the group 3) with aid from the EIS system on one hand and by conventional exams on the other. Patients were followed up for two months and had four control visits. (Visit 1 was before the treatment.)

Results of the EIS System and of conventional exams (laboratory tests, blood pressure measurement, and symptomatology) led to the creation of the following graphics (the raw data are in Excel files).

1. **Follow-up of thyroid substitute treatment**
   Population of 52 patients all diagnosed with hypothyroidism

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose</th>
<th>ESG graph segments 11/12 values and plots Fig.6</th>
<th>Laboratory TSH tests values and plots Fig.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1=(D)</td>
<td>No treatment</td>
<td>-40 +/- 10</td>
<td>9 +/- 2</td>
</tr>
<tr>
<td>Visit 2=(D+15)</td>
<td>100 µg</td>
<td>-10 +/- 5</td>
<td>6 +/- 1</td>
</tr>
<tr>
<td>Visit 3=(D+30)</td>
<td>120 µg</td>
<td>0 +/- 10</td>
<td>3 +/- 1</td>
</tr>
<tr>
<td>Visit 4=(D+45)</td>
<td>150 µg</td>
<td>+20 +/- 4</td>
<td>0.3 +/- 0.3</td>
</tr>
<tr>
<td>Visit 5=(D+60)</td>
<td>100 µg</td>
<td>-5 +/- 7</td>
<td>2 +/- 0.7</td>
</tr>
</tbody>
</table>

![Graph of 11-12 ESG](image.png)

*Figure 6*
Figure 8: Scatter gram of the values of numeric form of conductivity of the 11 and 12 ESG segments before treatment.

Figure 9: Scatter gram of Hypothyroidism indicators with EIS system (Numeric form of conductivity of the 11 and 12 ESG segments) and laboratory tests (TSH) before treatment.

\[ r^2 = 0.0825 \]  

This difference is considered to be not statistically significant.

\[ r^2 = 0.64 \quad P < 0.0001 \]
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**Figure 10**

Figure 10: Scatter gram of Monitoring values of Thyroid treatment with EIS system (Numeric form of conductivity of the 11 and 12 ESG segments) and laboratory tests (TSH)

$r^2 = 0.79$ $P<0.0001$

**2A. Follow-up of hypertensive treatment with beta-blockers**

Population of 37 patients all diagnosed with High blood pressure

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose</th>
<th>Volumes 2+14+15+17 of the ESG Graph values and plots Fig 11</th>
<th>blood pressure readings (systolic) values and plots Fig. 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1=D</td>
<td>No treatment</td>
<td>40+/- 8</td>
<td>157/+/- 7</td>
</tr>
<tr>
<td>Visit 2=D+15</td>
<td>50 mg once daily</td>
<td>-15+/- 12</td>
<td>139/+/- 5</td>
</tr>
<tr>
<td>Visit 3=D+30</td>
<td>50 mg once daily</td>
<td>-27+/- 15</td>
<td>133/+/- 10</td>
</tr>
<tr>
<td>Visit 4=D+45</td>
<td>50 mg once daily</td>
<td>-40+/- 10</td>
<td>126/+/- 9</td>
</tr>
<tr>
<td>Visit 5=D+60</td>
<td>50 mg once daily</td>
<td>-20+/- 11</td>
<td>129/+/- 12</td>
</tr>
</tbody>
</table>

**2-4-15-17 ESG**

$y = -14.5x + 31.1$

$R^2 = 0.5555$
Figure 11

Figure 12

Figure 13: Scatter gram of the values of numeric form of conductivity of the 2-4-15-17 ESG segments before treatment.
r² = 0.0417 this difference is considered to be not statistically significant.

Figure 14: Scatter gram systolic BP indicators with EIS system (Numeric form of conductivity of the 2-4-15-17 ESG segments) and conventional blood pressure measurement* before treatment
r² = 0.197 this difference is considered to be not statistically significant
Figure 15
Figure 15: Scatter gram of Monitoring values of Thyroid treatment with EIS system (Numeric form of conductivity of the 2-4-15-17 ESG segments) conventional blood pressure measurement*. $r^2 = 0.78$ P<0.0001.

* Material use for the measurement of the diastolic pressure: AllHeart Standard Blood Pressure: 3 measurements each 15 minutes and the lower BP selected
2. B Follow-up of hypertensive treatment with inhibitors of enzyme conversion (I.E.C.)

Population of 20 patients all diagnosed with High blood pressure

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose</th>
<th>Volumes of the ESG Graph values and plots Fig.16</th>
<th>blood pressure readings (diastolic) values and plots Fig.17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1=D</td>
<td>No treatment</td>
<td>+37+/−9</td>
<td>.../120+/−5</td>
</tr>
<tr>
<td>Visit 2=D+15</td>
<td>25 mg twice daily</td>
<td>−12+/−8</td>
<td>.../115+/−3</td>
</tr>
<tr>
<td>Visit 3=D+30</td>
<td>25 mg twice daily</td>
<td>−22+/−4</td>
<td>.../95+/−5</td>
</tr>
<tr>
<td>Visit 4=D+45</td>
<td>25 mg twice daily</td>
<td>−37+/−6</td>
<td>.../80+/−4</td>
</tr>
<tr>
<td>Visit 5=D+60</td>
<td>25 mg twice daily</td>
<td>−31+/−5</td>
<td>.../90+/−11</td>
</tr>
</tbody>
</table>

![6-8-19-21 ESG](image)

**Figure 16**

![Diastolic BP](image)

**Figure 17**
Figure 18
Figure 18: Scatter gram of the values of numeric form of conductivity of the 6-8-19-21 ESG segments before treatment.
r2 = 0.119 this difference is considered to be not statistically significant.

Figure 19
Figure 19: Scatter gram diastolic BP indicators with EIS system (Numeric form of conductivity of the 2-4-15-17 ESG segments) and conventional blood pressure measurement* before treatment.
r2 = 0.0515 this difference is considered to be not statistically significant.

Figure 20
Figure 20: Scatter gram of Monitoring values of Thyroid treatment with EIS system (Numeric form of conductivity of the 6-8-19-21 ESG segments) conventional blood pressure measurement*.
r2 = 0.72 P<0.0001.

* Material use for the measurement of the diastolic pressure: All Heart Standard Blood Pressure: 3 measurements each 15 minutes and the lower BP selected.
3. **Follow-up of patients using anticoagulants** (vitamin K antagonists’ oral mode)

Population of 49 patients all diagnosed with atherosclerosis and thrombosis risk.

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose</th>
<th>Volumes 6+13+19 of the ESG Graph values and plots Fig 21</th>
<th>Prothrombin Time values and plots Fig.22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1=D</td>
<td>No treatment</td>
<td>+23+/- 4</td>
<td>98-100 %</td>
</tr>
<tr>
<td>Visit 2=D+3</td>
<td>45 mg/day</td>
<td>-25+/- 5</td>
<td>38%+/- 2</td>
</tr>
<tr>
<td>Visit 3=D+9</td>
<td>45 mg/day</td>
<td>-30+/- 9</td>
<td>35 %+/- 2</td>
</tr>
<tr>
<td>Visit 4=D+12</td>
<td>45 mg/day</td>
<td>-30+/- 9</td>
<td>35%+/- 1</td>
</tr>
<tr>
<td>Visit 5=D+15</td>
<td>45 mg/day</td>
<td>-27+/- 7</td>
<td>35%+/- 1</td>
</tr>
</tbody>
</table>

![Figure 21](image1)

![Figure 22](image2)
**Figure 23**

Figure 23: Scatter gram of Monitoring values of anticoagulant treatment with EIS system (Numeric form of conductivity of the 6-13-19 ESG segments) and laboratory tests (Prothrombin Time)

$r^2 = 0.91 \ P<0.0001.$
4. Follow-up of patients using antidepressants (fluoxetine hydrochloride)
Population of 57 patients all diagnosed with Major depression

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose</th>
<th>Volumes 1+3+9+10+16+18 of the ESG Graph values and plots Fig 24</th>
<th>Symptomatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1=D</td>
<td>No treatment</td>
<td>-60 +/- 12</td>
<td>Depressed 100%</td>
</tr>
<tr>
<td>Visit 2=D+15</td>
<td>50mg /day</td>
<td>-60 +/- 6</td>
<td>No response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depressed 100%</td>
</tr>
<tr>
<td>Visit 3=D+30</td>
<td>50mg /day</td>
<td>-67 +/- 13</td>
<td>Response (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depressed 92%</td>
</tr>
<tr>
<td>Visit 4=D+45</td>
<td>50mg /day</td>
<td>-30 +/- 12</td>
<td>Responses (40%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depressed 60%</td>
</tr>
<tr>
<td>Visit 5=D+60</td>
<td>50mg /day</td>
<td>-20 +/- 10</td>
<td>Responses (65%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depressed 35%</td>
</tr>
</tbody>
</table>

![1-3-9-10-16-18 ESG](image)

**Figure 24**
Figure 25

Figure 26: Scatter gram of the values of numeric form of conductivity of the 1/3/9/10/16/18 ESG segments before treatment.

\[ r^2 = 0.0024 \] this difference is considered to be not statistically significant.

Figure 27: Scatter gram depression indicators with EIS system (Numeric form of conductivity of the 1/3/9/10/16/18 ESG segments) and % depressed patients (symptomatology)

\[ r^2 = 0.87 \ P<0.0001 \]
DISCUSSION AND CONCLUSIONS

Discussion
In the study, we found marked changes in the ESG segments’ values before and after drugs’ administration of thyroid, hypo tension, anticoagulant and SSRIs drugs.

This may have been caused by changes in:

- The ionograms:
  - With the interstitial potassium concentration change (marker of vasodilation\(^{(27)}\) which increased with the anticoagulant and CEI,
  - With Na\(^+\)/K\(^+\) ATPase pump increased with the thyroid treatment\(^{(28)}\) and decreased with the Beta blockers\(^{(29)}\),
  - With the sodium concentration which decreased with the SSRIs\(^{(30)}\).

- The interstitial fluid H\(^+\) concentration
- The Tissue oxygen delivery

The ESG segments values seem accurate for the monitoring of the drugs’ monitoring of the considered diseases:

Hypothyroidism:
Monitoring of the EIS system versus laboratory test (TSH) with the thyroid substitute treatment
\(r^2 = 0.79\ P<0.0001\).

High blood pressure:
Monitoring of the EIS system versus NIBP measurement with the Beta blockers treatment
\(r^2 = 0.78\ P<0.0001\).
Monitoring of the EIS system versus NIBP measurement with CEI treatment
\(r^2 = 0.78\ P<0.0001\)

Atherosclerosis and/or thrombosis risk:
Monitoring of the EIS system versus laboratory test (Prothrombin Time) with the anticoagulant treatment
\(r^2 = 0.91\ P<0.0001\)

Major depression:
Monitoring of the EIS system versus the depression’s symptomatology with the SSRIs treatment
\(r^2 = 0.87\ P<0.0001\)

The system is quite sensitive, permitting an evaluation of the effectiveness of the treatment and/or adjustment of dosages at low cost, immediate available results after the measurement and non invasive.

The problem that physicians find in private practice is a lack of drugs monitoring related to the price paid by the patient. The fact is that many of the hospitalizations have for cause the side effects of medications.\(^{(31)}\)
By this last point it represents a certain economization of costs related to health care in all interested countries.

**Limitations**

The ESG segments values can monitor the treatment of the considered diseases ($p < 0.001$) but they not diagnose the considered diseases. ($p$ is considered to be not statistically significant)

Therefore the ESG segments values should no to be use for diagnosis.

This clinical trial was performed in view of future publication.

**REFERENCES**


29) http://www.flash-med.com/Side_Effects_Effexor.asp