The ES TECK Screening System

TECHNIQUES

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Screening - up to date technique
In these digital times man expects his health and physiology status to be presented in digital and preferably visual ways. This explains the growing demand for easily performed health screening techniques.

Systems using digits, charts and other visual techniques further offer the valuable advantage of being motivating in terms of lifestyle changes as physiological deviations are shown in an educating way. In many cases, lifestyle improvements are inevitable in order to prevent or reduce or eliminate signs of illness.

Along with the screening results, the state-of-the art scientific technology ES Teck also provides information required for recommending effective preventive efforts. When viewing and comparing the images from the screenings prior to and after preventive interventions (follow-up panels are included,) the guest will feel motivated to continue with his/her health efforts.

The ES Teck Screening System
ES Teck is a computer-aided medical system for assessing the functional health status of the body in general or for specific body systems. It is used as a stable reference point in monitoring and developing any treatment as it is highly reliable. A complete piece of software is used to create pictures, diagrams and graphs personal to the patient.

The screening procedure is noninvasive. It takes 5 minutes and provides approximately 70 different physiological parameters.

ES Teck is a screening technology. It is not a diagnostic tool but rather provides assessment data that may be used for recommending individualized, safe and effective health measures. As the screening results are displayed on a computer screen they can be viewed by both the practitioner and the guest. The development of the results over time also can be viewed on the screen. Prior to starting the screening, the practitioner puts in information on the guest’s height, weight and blood pressure. During the screening procedure five various measurements are performed by means of two measuring methods; oximeter and the electro interstitial scan-GS (EIS-GS) which is an impedance measurement method. Although two measuring methods are used, the guest will experience the screening as one single measurement.

The ES Teck Screening Techniques
The ES Teck System combines various techniques:

Oximeter
Data obtained by the oximeter:
- HRV- Heart Rate Variability – Heart and Autonomic Nervous System
  Estimation of pulse/heart rate. The heart rate variability is the intervals between the heart beats. These intervals should be neither too long (arrhythmia) nor too short (decreased heart rate variability, HRV). A decreased HRV is a verified marker of illness/disease.
  HRV is also an indirect assessment of the autonomic nerve function, i.e. the balance
between sympathetic and parasympathetic activity of the autonomic nervous system. According to certain research the HRV also provides information about breathing. The clinical HRV trials and research have focused on neurological and cardiological applications.

- **Oximeter – Oxygen (SpO₂)**
  Two various frequencies of light; infrared light and red light are used to measure to kinds of hemoglobins; oxygen-saturated hemoglobin and hemoglobin without oxygen.

- **Pulse plethysmography waveform – circulation**
  The plethysmography is a physiologic measuring technique studied within bio-optics. Researchers say this kind of non-invasive digital pulse waveform analysis will be increasingly used, also for evaluation of heart medication and epidemiologic research on coronary heart diseases. As the heart contracts and the blood is pushed into the artery, an arterial pulse waveform is generated. The peripheral pulse waveform reflects volume changes in the artery, which is why mathematical calculations can be used to make assessments relating to blood flow and circulation, for instance stiffness markers of the vascular system may be estimated. Since the state of the endothelium is the same throughout the body, the values of the blood measured in the fingertip is true for the rest of the endothelium, i.e. dysfunctions observed in the fingertip are in fact systemic dysfunctions.

**Galvanic Skin Responses – EIS GS**

The electrical conductance of the skin is related to the function of the sweat glands and can be measured by GRS, galvanic skin responses devices or by EDR, electrodermal response devices. The technique is similar to EEG and ECG. The sweat glands are controlled by the sympathetic nervous system through noradrenalin and cholinergic nerve transmission. Hence, skin conductance indicates psychological and/or physiological arousal.

The EIS-GS, Electro Interstitial Scan – Galvanic Skin, is a part of the ES Teck System and is classified as a GSR device. It has been designed on scientific knowledge about bioimpedance and electrochemical redox reaction analysis with the objective to correctly interpret the results of the conductance measurements as markers of disease or as indicators of treatment responses. Tissue indications on the status of certain tissues and organs are obtained by using existing knowledge about the properties of electrical conductance in living tissue. Chronic or acute inflammation are examples of such indications.

During the bioimpedance measurement very weak electrical impulses are sent through the interstitial fluid of the body. Depending on how the impulses travel through the fluid various data can be obtained. In other words, the bioimpedance wave propagation is related to the interstitial morphology and density. The conductivity is proportional to the ATP production in the cell mitochondria. The EIS GS evaluates the sympathetic system activity with the FFT calculation of the conductance values as shown in clinical investigation performed by the University of Miami.

Using six tactile electrodes, a weak DC current is sent alternatively between two electrodes with a sequence. The EIS GS device records the electrical conductance of eleven various pathways of the body. The conductance measurements are sent to and saved on a PC for signal processing analysis and follow up.
Bioimpedance Analysis
Bioelectrical impedance analysis, BIA, is a widely used technique for estimating body composition. The technique is quick, portable, inexpensive and noninvasive.
The body composition is estimated by using the resistance and reactance measurements of the human body in tetrapolar mode and in mono frequency of 50 KHz together with the appropriate algorithms from peer reviews.
In the human body, low resistance is associated with large amounts of fat free mass and low fat mass. Vice versa, high resistance is associated with smaller amounts of fat free mass and high fat mass.
High reactance is associated with large amounts of body cell mass (intracellular mass) and low extracellular water, ECW. Vice versa, low reactance is associated with smaller amounts of body cell mass and high ECW.

Algorithms
Whereas the EIS GS technology provides measuring data relating to the sympathetic system activity, other data are calculated on the basis of electrochemical principles, peer reviews, trials (in vitro and animal) and clinical investigations.
Indirect parameters are obtained by combining measurement data with scientific data on the human physiology. Hence, some ES Teck parameters are based on algorithms.

Approvals

Electro Sensor – Oxi
FDA Clearance 510k number 102442 /CE Mark
US FDA 21 CFR 870.2700 / 2300 Product Code: DQA, MWI
Classification: Class II
Classification Panel: Cardiovascular /Anesthesiology
Canadian MDR P.C. 1998-783 Class III
Australian TGA (ARGMD) Class II
MDD/93/42EEC Class II a Product code MD 1100 GMDN Code: 17146

Electro Sensor – EIS GS:
FDA Clearance 510k number 102177 /CE Mark
System component: 21 CFR 882.1540 Product Code: GZO
Classification: Class II Classification Advisory: Neurology
MDD/93/42EEC Class II a Product code MD 1100 GMDN Code: 32588
Australian TGA (ARGMD) Class II

Electro Sensor – BC
FDA Clearance 510k number 103026 /CE Mark
Advisory: Cardiovascular
21 CFR Sec. 870.2770: Impedance Plethysmograph Class II (performance standards).
Product code: DQA/MNW
MDD/93/42EEC Class II a Product code MD 1100 GMDN Code: 36022
Medical devices EIS-GS, ESO and ES-BC - clinical validation

References (1)
Comparing the accuracy of ES-BC, EIS and ES Oxi results versus the recognized standardized assessment. (1)

R&D Publications EIS-GS

References (2-5)
Electro interstitial scan system: assessment of 10 years of research and development. (2)

Bioimpedance Chronoamperometry as an adjunct to prostate-specific antigen screening for prostate cancer. (3)
Abreu D.S.
Cancer Management and Research 2011:3 109–116

Bioimpedance Application in Selective Serotonin Reuptake Inhibitor (SSRI) treatment monitoring (4).
Aleexev V.G and Kuznecova L.V.

New marker using bioimpedance technology in screening for Attention Deficit/Hyperactivity Disorder (ADHD) in Children as adjunct to conventional diagnostic methods. (5)
Caudal F.
Galvanic skin responses

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Vitale GI, Quatrale R.P., Giles P.J, Birnbaum J E.

Joines W, Zhang Y, Chenxing L, Randy L. The measured electrical properties of normal and malignant human tissues from 50 to 900 MHz (27)
Tillgänglig: http://online.medphys.org/resource/1/mphya6/v21/i4/p547_s1?isAuthorized=no.


We assessed sympathovagal balance in thyrotoxicosis. Fourteen patients with Graves' hyperthyroidism

Plasma catecholamine concentrations in hyperthyroidism and hypothyroidism (33)
Diabetes, insulin resistance

Clinical Investigations

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**Clinical investigation reference**

**ROC Curve**

Correlation between HOMA2 and HbA1c with algorithms based on distinct physiologic measurements (ES Complex software) Authors: Dr. Chaim Elinton Adami, Renata Cristina Gobato and Prof. Dr. Marcelo de Carvalho Ramos – UNICAMP-Brazil

ESC cutoff values for defining metabolic syndrome based on results obtained from contingency analysis and ROC curves are 3.0. For Metabolic Syndrome diagnosis the area under the curve obtained was 0.9413

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### Blood Glucose Control screening test: Correlation ESC-IR / Homa2-IR

Results: We found HOMA2-IR to be strongly correlated with ESC-IR (R=0.83 P=0.0001).
ESC-IR cutoff values for defining Insulin Resistance based on results obtained from contingency analysis and ROC curves are 2.5. For Insulin Resistance 0.9022

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### β cell function screening test: Correlation ESC-% β algorithm and HOMA2-% β

Results: Correlation of ESC-% β algorithm and HOMA2-% β The coefficient of correlation ESC-% β and HOMA2-%β is r=0.72 and significance level p < 0.0001.

!!! The screening score should be not considered if the patient is undergoing insulin or secretagogues treatments
Oximeter – pulsplethysmography - HRV (ref. 34-65)
Frequency Domain Analysis of Heart Rate Variability and their Correlations in Diabetes (34)
P. T. Ahamed Seyd, V. I. Thajudin Ahamed, Jeevamma Jacob, Paul Joseph K.
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Cardiovascular Division, Washington. University School of Medicine, St. Louis, Missouri 63108, USA.

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Diabetes Care December 1998 vol. 21 no.12 2116-2122.

Decreased heart rate variability may predict the progression of carotid atherosclerosis in type 2 diabetes (38)
Gottsater A, Ahlgren AR, Taimour S, Sundkvist G.

Decrease heart rate variability but preserve postural blood pressure change in type 2 diabetes with microalbuminuria (39)

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Perciaccante A, Fiorentini A, Paris A, Serra P, Tubani L.
BMC Cardiovasc Disord. 2006 May 2;6:19.

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Sun TB, Yang CC, Kuo TB.

Differences in heart rate variability in non-hypertensive diabetic patients correlate with the presence of underlying cerebrovascular disease (43)

Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy (44)
Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH.

Heart rate variability and circadian variations in type 1 diabetes mellitus (45)
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Relationships between heart rate variability and urinary albumin excretion in patients with type 2 diabetes (46)
Takebayashi K, Matsutomo R, Matsumoto S, Suetsugu M, Wakabayashi S, Aso Y, Inukai T.
Comparison of fast Fourier transform and autoregressive spectral analysis for the study of heart rate variability in diabetic patients (47)
Chemla D, Young J, Badilini F, Maison-Blanche P, Affres H, Lecarpentier Y, Chanson P.

Parasympathetic versus sympathetic control of the cardiovascular system in young patients with type 1 diabetes mellitus (48)
Javorka M, Javorkova J, Tonhajzerova I, Javorka K.

Adiponectin concentrations in sera from patients with type 2 diabetes are negatively associated with sympathetic balance as evaluated by power spectral analysis of heart rate variation (49)
Wakabayashi S, Aso Y.

Cardiac autonomic balance and QT dispersion during head-up tilt testing in diabetics with and without sensory neuropathy (50)
Tanikawa T, Abe H, Tanaka Y, Nakashima Y.

Power spectral analysis of heart rate variability in patients with Charcot's neuroarthropathy (51)

Application of heart rate variability in prognosis of patients with diabetes mellitus (52)
Markuszewski L, Bissinger A.

Analysis of the chaotic component of the sinusal R-R intervals as a tool for detecting a silent cardiac dysautonomia in type 2 diabetes mellitus (53)

Heart rate variability analysis: a tool to assess cardiac autonomic function (54)
Lewis MJ.

Circadian rhythm of autonomic activity in non diabetic offsprings of type 2 diabetic patients (55)
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Pre-operative measurement of heart rate variability in diabetics: a method to estimate blood pressure stability during anaesthesia induction (62)
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Role of heart rate variability in the early diagnosis of diabetic autonomic neuropathy in children (65)

Bioimpedance (ref. 65-66)
New Approach to beta cell function screening by nitric oxide assessment of obese individuals at the population level (66)
Chaim E A, Gobato R C,

Correlation between HOMA2 and HbA1c with algorithms derived from bioimpedance and spectrophotometric devices (67)
Chaim E A, Gobato R C, Carvalho Ramos M.
Correlation between physiological data algorithms with the homeostasis model assessment (HOMA) and with blood glycated hemoglobin (HbA1c) (68)
Chaim Elinton Adami and Renata Cristina Gobato. Unicamp University 2011

Increased Fat Mass Compensates for Insulin Resistance in Abdominal Obesity and Type 2 Diabetes (69)
Diabetes September 2005 vol. 54 no.9 2720-2726

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Miyazaki Y, Glass L, Triplitt C, Wajcberg E, Mandarino LJ, DeFronzo RA.

Insulin resistance and hypersecretion in obesity: European Group for the Study of Insulin Resistance (EGIR) (72)
Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G.

Hepatitis

Clinical Investigations
New approach for large scale screening for the asymptomatic Hepatitis C Virus (HCV) (73)
Dr Yamanaka, Ademar. Unicamp University Brazil 2011.

Cardiac Autonomic Dysregulation in Patients with Acute Hepatitis (74)
Chen, Kuan-Yang MD; Chen, Chien-Lin MD; Yang, Cheryl C. H PHD; Kuo Terry B.J. MD, PHD.

QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium (75)
Simonetta Genovesi*†, Daniela M. Prata Pizzala‡, Massimo Pozzi‡, Laura Ratti†, MariaMilanese‡,

Chronic hepatitis C virus infection associated with autonomic dysfunction (76)
Osztovits, J., T. Horváth, and L. Littvay.
Prostate cancer screening

Clinical Investigations

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<th>Disease Screening Score</th>
<th>Suggested supplementary examinations</th>
<th>Follow Up</th>
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<tr>
<td>Prostate cancer EIS + PSA</td>
<td>N/A without Lab test. Click here to enter PSA value.</td>
<td>PSA</td>
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<td>Prostate cancer EIS</td>
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Prostate cancer screening EIS + PSA test: Specificity and sensitivity

Clinical investigation reference


Other references (ref. 77)


Depression and mode

Clinical Investigations

Cerebral neurotransmitters and thyroid response

Cerebral serotonin response

Cerebral dopamine and Noradrenaline response

Cerebral GABA responses

Thyroid response

Cerebral Serotonin response screening test: Specificity and sensitivity Response / markers

Clinical investigation reference


At day 45, 2 groups where constituted: group 1: group with treatment response and group 2: group with non treatment response. At day 60, 2 groups where constituted: group 3: group with treatment response and group 4: group with non treatment response
Results:
Comparing the group 1 and 2, electrical conductivity measurement of the pathway between the 2 disposable forehead electrodes has a specificity of 72% and a sensitivity of 85.3% (p < 0.0001) with a cutoff of 4.32 μS. Comparing the group 3 and 4, electrical conductivity of the same pathway has specificity of 47.6% and a sensitivity of 76.3% (p < 0.16) with a cutoff of 5.92 μS. Comparing the group 1 and 2, electrical dispersion a parameter of the pathway between the 2 disposable forehead electrodes has a specificity of 80% and a sensitivity of 85.2% (p < 0.0001) with a cutoff of 0.678. Comparing the group 3 and 4, electrical dispersion a parameter of the same pathway has specificity of 100% and a sensitivity of 89.5% (p < 0.0001) with a cutoff of 0.692.

Cerebral Noradrenaline and dopamine response screening test: correlation Response/ markers

Clinical investigation references
Gavin Lambert, PhD: Mats Johansson, MD, PhD: Hans Ågren, MD, PhD: Peter Friberg, MD, PhD Reduced Brain Norepinephrine and Dopamine Release in Treatment-Resistant Depressive Illness Arch Gen Psychiatry. 2000; 57:787-793.

Results: The brains of three patients exhibited reduced venous arterial norepinephrine (3.4 ± 2.7 nmol/L vs. 0.7 ± 1.3 nmol/L) and homovanillic acid concentration gradient (8.3 ± 7.8 nmol/L vs. 3.1 ± 1.9 nmol/L), associated energy source other than glucose. Intracellular pH, hydroxyproline, and concentration gradient were not reduced in the patients with depression-naïve. While both the reduction in serotonin turnover and the deficit in cerebral metabolism were normalized following pharmacological blockade of the norepinephrine transporter with desipramine, paradoxically it was the brain content of dopamines that bore a significant relationship to the patient's clinical status (r = 0.79, P = .02). The positive nature-of this relationship remains difficult to reconcile.


Results: Changes in striatal extracellular dopamine (DA) in the anoxic turtle are addition of the specific DA transport blocker GBR 12909 or the sodium potassium adenosine triphosphatase (Na/K-ATPase) blocker ouabain. Mean percent change standard deviation, N = 6 per group. Paired t-test indicate significantly different means (P < 0.05).

Cerebral GABA response screening test: correlation Response/ Cl- conductance

Clinical investigation reference

a. The effects of brief and prolonged GABA application upon rat paratraceal neurons. Rapid depolarization induced by brief (0.05s) ionoinphoretic applications of GABA, the total charge ejected in each case is indicated in nC below the responses. Downward deflections are the membrane voltage responses to constant hyperpolarizing current pulses (100pA, 50ms) used to

b. The current-voltage relationships for the cell in the presence of GABA. The point of intersection of the two curves gives a value for the equilibrium potential (E) for sustained current response of approximately -38 mV.

Other references (ref. 78)
Bioimpedance application in Selective serotonin reuptake inhibitors (SSRIs) treatment monitoring (4)
ADHD Children

Clinical Investigations

<table>
<thead>
<tr>
<th>ADHD children (learning)</th>
<th>Disease Screening Score</th>
<th>Suggested supplementary examinations</th>
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<td>According to the clinical context</td>
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ADHD learning disability screening test: Specificity and sensitivity


Results: The conductivity measurements of the pathway of the forehead electrodes have a specificity of 98% and a sensitivity of 80% with a cut off > 7.4µSI and P< 0.0001.

Other references (ref. 78-82)

Pediatrics New marker using the bioimpedance technology in Attention Deficit/Hyperactivity (78) Disorder (ADHD) Children screening in adjunct to the conventional diagnostic methods. Dr. Frederique Caudal, Caudal 2007 (France)


Heart Rate Variability and Sustained Attention in ADHD Children (80) Norbert Börger, Jaap van Der Meere, Arjen Ronner, Ed Alberts, Reint Geuze and Hans Bogte.


Dyslipidemia, cardiovascular diseases, coronary heart diseases and carotid stiffness

Clinical Investigations

<table>
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<th>Cardiovascular diseases</th>
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<td>Lipid Cholesterol</td>
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<td>LV Hypertrophy</td>
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**Arterial Atheroma screening test: Specificity and sensitivity**

**Clinical investigation references**


According to the clinical investigation results, the parameter b of the SDPTG is using only for Women.

<table>
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<tr>
<th>Cut-off value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.53</td>
<td>0.85</td>
<td>0.58</td>
</tr>
<tr>
<td>Female</td>
<td>0.40</td>
<td>0.83</td>
<td>0.72</td>
</tr>
</tbody>
</table>


For men and women we use the parameter Reflection Index (RI) of the SDPTG. This parameter is specific and sensitive, but cannot detect the severity of the CDH grade.

The mean value of RI for no-CAD group was 37.82% ± 7.3% vs. CAD group 70.09% ± 10.09% (p = 0.001) and the mean value of SVI is 8.00 ± 0.93 m/s for no-CAD group vs. 9.52 ± 1.03 m/s for CAD group (P = 0.005)

**Clinical investigation reference**


**Correlation Table**

<table>
<thead>
<tr>
<th></th>
<th>HR (min⁻¹)</th>
<th>PSBP (mm Hg)</th>
<th>PDBP (mm Hg)</th>
<th>PPP (mm Hg)</th>
<th>Aix (%)</th>
<th>Avg (mm Hg)</th>
<th>T_R (ms)</th>
<th>CSBP (mm Hg)</th>
<th>CDBP (mm Hg)</th>
<th>CPP (mm Hg)</th>
<th>PPP:CPP (Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>70 ± 9</td>
<td>132 ± 15</td>
<td>84 ± 11</td>
<td>49 ± 12</td>
<td>24.8 ± 11.3</td>
<td>9.9 ± 5.9</td>
<td>140 ± 13</td>
<td>122 ± 17</td>
<td>85 ± 12</td>
<td>37 ± 11</td>
<td>1.34 ± 0.25</td>
</tr>
<tr>
<td>Controls</td>
<td>74 ± 12</td>
<td>131 ± 15</td>
<td>84 ± 11</td>
<td>47 ± 13</td>
<td>15.6 ± 12.1</td>
<td>5.8 ± 5.3</td>
<td>145 ± 11</td>
<td>118 ± 17</td>
<td>85 ± 11</td>
<td>33 ± 10</td>
<td>1.45 ± 0.24</td>
</tr>
<tr>
<td>Significance</td>
<td>0.062</td>
<td>0.6</td>
<td>1.0</td>
<td>0.5</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.0013</td>
<td>0.1</td>
<td>0.9</td>
<td>0.028</td>
<td>0.012</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SD.

Aix = augmentation index; Avg = systolic augmentation; CDBP = central diastolic blood pressure; CPP = central pulse pressure; CSBP = central systolic blood pressure; HC = hypercholesterolemia; HR = heart rate; PDBP = peripheral diastolic blood pressure; PPP = peripheral pulse pressure; PSBP = peripheral systolic blood pressure.
Multiple metabolic syndrome is associated with lower heart rate variability (82)

The Atherosclerosis Risk in Communities Study

Vasoactive Agents and Vascular Aging by the Second Derivative of Photoplethysmogram Waveform (83)
Takazawa, Kenji; Tanaka, Nobuhiro; Fujita, Masami; Matsuoka, Osamu; Saiki, Tokuyu; Aikawa, Masaru; Tamura, Sinobu; Ibukiyama, Chiharu.

Independent Determinants of Second Derivative of the Finger Photoplethysmogram among Various Cardiovascular Risk Factors in Middle-Aged Men (84)
Toshiaki Otsuka, Tomoyuki Kawada, Masao Katsumata, Chikao Ibuki, and Yoshiki Kusama.
Utility of Second Derivative of the Finger Photoplethysmogram for the Estimation of the Risk of Coronary Heart Disease in the General Population (85)
Toshiaki Otsuka, , Tomoyuki Kawada, Masao Katsumata, and Chikao Ibuki.
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R. Kelly, MB, Fracp, C. Hayward, MB, BSc, A. Avolio, PhD, and M. O’Rourke, MD, Facc.

Excess accumulation of body fat is related to dyslipidemia in normalweight subjects (87)
Ito H, Nakasuga K, Ohshima A, Sakai Y, Maruyama T, Kaji Y, Harada M, Jingu S, Sakamoto M.

The influence of the peripheral reflection wave on left ventricular hypertrophy in patients with essential hypertension (88)
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Hypertens Res 2000 Sep 23:451-8

Aortic Stiffness Is an Independent Predictor of Primary Coronary Events in Hypertensive Patients. A Longitudinal Study (89)
Pierre Boutouyrie, Anne Isabelle Tropeano, Roland Asmar, Isabelle Gautier, Athanase Benetos, Patrick Lacolley, Stephane Laurent.

Evaluation of a Noninvasive, Widely Applicable Method for Assessing Endothelial Function (90)

Aortic stiffness as a risk factor for recurrent acute coronary events in patients with ischemic heart Disease (91)
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Hippokration Hospital, Department of Cardiology, University of Athens, Greece.
Abstracts

1. Comparing the accuracy of ES-BC, EIS and ES Oxi results versus the recognized standardized assessment.

Background and Purpose:
The Electro Sensor Complex (ESC) is software that combines three devices using bioelectric impedance, galvanic skin response, and spectrophotometry: (1) ES-BC to assess body composition, (2) EIS to predict autonomic nervous system activity, and (3) ES Oxi to assess cardiac output. The objective of this study was to compare each to a standardized assessment: ES-BC to dual-energy x-ray absorptiometry (DEXA), EIS to heart rate variability (HRV), and ES Oxi to BioZ Dx.

Patients and methods:
The study was conducted in 2 waves. Fifty subjects were assessed for body composition and autonomic nervous system activity. Fifty-one subjects were assessed for cardiac output.

Results:
We found adequate relative and absolute agreement between ES-BC and DEXA for fat mass (r=0.97, p<0.001) with ES-BC overestimating fat mass by 0.2 pounds and for body fat percentage (r=0.92, p<0.001) with overestimation of fat percentage by 0.4%. For autonomic nervous system activity, we found marginal relative agreement between EIS and HRV by using EIS as the predictor in a linear regression equation (adjusted $r^2=0.56$, p=0.03). For cardiac output, adequate relative and absolute agreement was found between ES Oxi and BioZ Dx at baseline (r=0.60, p<0.001), after the first exercise stage (r=0.79, p<0.001), and after the second exercise stage (r=0.86, p<0.001), respectively. Absolute agreement was found at baseline and after both bouts of exercise; ES Oxi overestimated baseline and stage 1 exercise cardiac output by 0.3 and 0.1 l/min, respectively, but exactly estimated stage 2 exercise cardiac output.

Conclusion:
ES-BC and ES Oxi accurately assessed body composition and cardiac output compared to standardized instruments, whereas EIS showed marginal predictive ability for autonomic nervous system activity. The ESC software managing the 3 devices would be useful to help detect complications related to metabolic syndrome, diabetes, and cardiovascular disease and to non-invasively and rapidly manage treatment follow-up.

2. Electro interstitial scan system: assessment of 10 years of research and development.

Ten years of research and development have allowed an understanding of how the electro interstitial scan (EIS) works and what its clinical applications may be.

Materials and methods:
The EIS is a galvanic skin response device. The measurements are performed by electrical stimulation of the post sympathetic cholinergic fiber with weak DC current and voltage 1.28V applied during 2 minutes and in bipolar mode.

Current scientific knowledge:
EIS electrical measurements are related to: (1) the concentration of free chloride ions in the interstitial fluid, which affects the transfer of electrical current and the ratio intensity/voltage; (2) the morphology of the interstitial fluid, which is related to the electrical dispersion calculated from the Cole equation ($\alpha$ parameter); (3) electrical stimulation, which causes a change in sweat rate at the passive electrodes – post sympathetic cholinergic fiber electrical stimulation appears to be responsible for activating M2 receptors, which regulate nitric oxide (NO) production in the endothelial cell and cause vasodilation and a released sweat response; and (4) the electrochemical redox reactions (electrolysis) of the released sweat on electrodes, which are different on the bulk of the metal electrodes (O2 + [4H+] + [4e-]) and on the Ag/AgCl disposable electrodes (AgCl precipitation).

Results:
For each of the EIS clinical results, various explanations were posited, such as: (1) electrical stimulation of the postsympathetic cholinergic fiber-activating NO production in the endothelial cell, which causes vasodilation and a released sweat response (diabetes detection); (2) estimation of interstitial fluid's acid-base balance, which is reflected in an electrochemical reaction on the bulk of the electrodes through the released sweat (prostate cancer detection); (3) estimation of cerebral interstitial fluid chloride ions (detection of ADHD in children); and (4) estimation of the morphology of the interstitial fluid (selective serotonin reuptake inhibitor treatment response).

Conclusion:
After 10 years of development, the analysis of current scientific knowledge and results of clinical investigations have allowed a better understanding of EIS electrical measurements.

2. New Approach to beta cell function screening by nitric oxide assessment of obese individuals at the population level

Background:
Approximately 27% of Americans today are obese, and this condition increases the prevalence of metabolic syndrome and diabetes. The UK Prospective Diabetes Study suggests that loss of beta cell function can begin at least 10 years before diagnosis, and mean beta cell function is already less than 50% at diagnosis. The aim of this research was to assess the possibility of detecting loss of beta cell function in obese patients by a novel approach involving nitric oxide assessment using a combination of technologies.

Materials and methods:
One hundred and fifteen obese patients (93 women, 22 men) of mean age 39 (range 17–62) years, who were candidates for bariatric surgery were included in the study, and underwent laboratory tests, including fasting blood glucose, fasting insulin plasma, and examination with the Electro Sensor complex. The Electro Sensor complex offers a new way to assess nitric oxide production using five technologies managed by software, ie, the galvanic skin response, photoelectrical plethysmography, heart rate variability analysis, bioimpedance analysis, and blood pressure oscillometric measurements. The homeostasis model assessment 2% beta cell function (HOMA2% β) algorithm was calculated from fasting blood glucose and fasting insulin plasma using free software provided by The University of Oxford Diabetes Trial Unit.

The Electro Sensor complex percent beta (ESC% β) algorithm was calculated from the Electro Sensor complex data and statistical neural network. Statistical analysis was performed to correlate ESC% β and HOMA2% β using the coefficient of correlation and Spearman’s coefficient of rank correlation. Receiver-operating characteristic curves were also constructed to determine the specificity and sensitivity of ESC% β in detecting a HOMA2% β value, 100.

Results:
The coefficient of correlation between ESC% β and HOMA2% β was 0.72 (using log values) and the Spearman’s coefficient of rank correlation (rho) was 0.799 (P, 0.0001). ESC% β had a sensitivity of 77.14% and specificity of 78.21% (cutoff # 157, corresponding to 40% after conversion into a 0%–100% scale) to detect a HOMA2% β value, 100 (P, 0.0001).

Conclusion:
The ESC% β algorithm has a high predictive correlation with HOMA2% β, and good specificity and sensitivity to detect a HOMA2% β value, 100. Therefore, the Electro Sensor complex enabling nitric oxide assessment represents a novel method of screening for beta cell function in the obese population on a large scale. Such a tool, which is easy to administer, noninvasive, and cost-effective, would be of great benefit for widespread screening of beta cell function in obese patients.
3. Bioimpedance Chronoamperometry as an adjunct to prostate-specific antigen screening for prostate cancer.

**Background:**
Bioimpedance is an electrical property of living tissue that has been shown to be a safe technique when used in a number of biomedical applications. The aim of this research was to assess the utility of bioimpedance measurement as a rapid, cost-effective, and non invasive adjunct to digital rectal examination and PSA in differentiating tumor from normal prostatic tissue.

**Methods:**
Three hundred men were examined for signs and symptoms of prostate disorder. 147 patients with a digital rectal examination indicating a positive result underwent a prostate-specific antigen (PSA) test. A biopsy was advised for 103 of the men, of whom 50 completed the study. Before undergoing biopsy, an examination with the EIS (electro interstitial scan) system using bioimpedance and chronoamperometry was performed. In reference to the biopsy results (negative or positive), a statistical analysis of the EIS data and PSA was conducted using receiver operating characteristic curves to determine the specificity and sensitivity of each test.

**Results:**
The PSA test had a sensitivity of 73.9% and specificity of 51.9% using a cutoff value > 4 and a sensitivity of 52.2% and specificity of 81.5% using a cutoff value ≥ 5.7 and \( P = 0.03 \). The delta of the electrical conductivity (DE) of the left foot-right foot pathway had a sensitivity of 62.5% and specificity of 85.2%, with a cutoff value ≤ -5 and \( P = 0.0001 \). Algorithms comprising the delta of electrical conductivity and PSA showed a sensitivity of 91.5% and a specificity of 59.3%, with a cutoff value ≤ -10.52 and \( P = 0.0003 \).

**Conclusion:**
The EIS system had a very good specificity of 85.2%. However, the sensitivity of 62.5% would be a problem. Using a PSA reference > 4.1 ng/mL, the adjunctive use of bioimpedance and chronoamperometry provided by EIS technology could raise the sensitivity from 73.9% to 91.5% and the specificity from 51.9% to 59.3% in prostate cancer screening.

4. Bioimpedance Application in Selective Serotonin Reuptake Inhibitor (SSRI) treatment monitoring

**Background:**
Bioimpedance has been shown to be a safe technique when used in a number of biomedical applications. In this study, we use a device named Electro Interstitial Scan (EIS) performing bioimpedance measurements to follow up the effect of SSRI treatment in depressed subjects.

**Method and material:**
Fifty nine subjects (Age 47 from 17 to 76 years old and 38 women) diagnosed with major depression disorder by psychiatric assessment at the Botkin Hospital according to DSM-IV and CGI (Clinical Global Impression) were recorded with the EIS System before undergoing anti depressant SSRI treatment. Then, SSRI treatment follow-up was undertaken on one hand with the EIS bioimpedance measurements (electrical conductivity and dispersion \( \alpha \) parameter) and on the other hand by treatment responses based on Hamilton Depression Scale (Ham-D) and CGI each 15 days during 60 days.

At day 45, 2 groups where constituted: group 1: group with treatment response and group 2: group with non treatment response. At day 60, 2 groups where constituted: group 3: group with treatment response and group 4: group with non treatment response.

**Results:**
Comparing the group 1 and 2, electrical conductivity measurement of the pathway between the 2 disposable forehead electrodes has a specificity of 72 % and a sensitivity of 85.3% (\( P< 0.0001 \)) with a cutoff > 4.32µSi. Comparing the group 3 and 4, electrical conductivity of the same pathway has specificity of 47.6 % and a sensitivity of 76.3% (\( P< 0.16 \)) with a cutoff > 5.92µSi.

Comparing the group 1 and 2, electrical dispersion \( \alpha \) parameter of the pathway between the 2 disposable
forehead electrodes has a specificity of 80% and a sensitivity of 85.2% (p< 0.0001) with a cutoff > 0.678. Comparing the group 3 and 4, electrical dispersion $\alpha$ parameter of the same pathway has specificity of 100% and a sensitivity of 89.5% (p< 0.0001) with a cutoff > 0.692.

Conclusion:
The EIS electrical conductivity measurement of the forehead pathway has a high specificity and sensitivity at D+ 45 comparing the patients’ response group and non response group. The specificity and sensitivity decrease at D+60.
The EIS electrical dispersion $\alpha$ parameter of the forehead pathway has a high specificity and sensitivity at D+ 45 comparing the patients’ response group and non response group. The specificity and sensitivity raise at D+60. The practitioners could therefore have available in the EIS System, a non-invasive, low-cost system that is easy to use in the office and that could offer major depression disorder treatment monitoring in adjunct to DSM-IV questionnaires and CGI.

5. New marker using bioimpedance technology in screening for Attention Deficit/Hyperactivity Disorder (ADHD) in Children as adjunct to conventional diagnostic methods.

Background:
Diagnosis of attention deficit/hyperactivity disorder (ADHD) in children is not straightforward and misdiagnosis may occur, which leads to the possibility of errors in treatment, with numerous possible side effects that could be especially damaging in view of the age of the population. For this reason, a tool that is easy to use, fast, and cost-effective, which provides an addition to conventional diagnosis and treatment monitoring of ADHD children, is needed. In this study, electro interstitial scans (EIS) were used to perform bioimpedance measurements.
The results of conductivity measurements taken using forehead electrodes in a group of children conventionally diagnosed with ADHD and in a control group not showing any symptoms of ADHD were compared.

Method:
Sixty children without any ADHD symptoms (group 1) and 52 children diagnosed with ADHD following psychiatric examination (group 2) underwent an examination with the EIS system. Statistical analysis was performed to compare the conductivity measurements at the level of the forehead electrodes, using independent $t$-tests and a receiver-operating characteristic curve (ROC) to determine the specificity and sensitivity of the test.

Results:
The mean of the conductivity measurements of two pathways between the forehead electrodes (from left forehead to right forehead and from right forehead to left forehead) in the ADHD group was 33.11 micro Siemens (mS) (range 2–113 mS). This was significantly higher ($P < 0.001$) than mean of the conductivity measurements of two pathways between the forehead electrodes of the control group (2.75 mS, range 1.75–27.4 mS).
In terms of the ROC results, comparing the two groups using the reference of the mean of conductivity measurements of the two pathways between the forehead electrodes, the test showed a specificity of 98% and sensitivity of 80% and $P = 0.0001$ (95% confidence interval) with a cutoff value at 7.4 mS.

Conclusion:
The EIS marker related to the conductivity measurements of the forehead pathway has a high specificity and high sensitivity and use of this could provide practitioners with a noninvasive, low-cost system that is easy to use in the office and could offer an adjunct to the conventional diagnosis of ADHD children. It could also assist in treatment monitoring, and allow for earlier intervention.

28. Hyperthyroidism is Characterized by Both Increased Sympathetic and Decreased Vagal Modulation of Heart Rate: Evidence From Spectral Analysis of Heart Rate Variability

Objective:
The clinical manifestations of hyperthyroidism resemble those of the hyperadrenergic state. This study was designed to evaluate the impact of hyperthyroidism on the autonomic nervous system (ANS) and to investigate the relationship between serum thyroid hormone concentrations and parameters of spectral heart rate variability (HRV) analysis in hyperthyroidism. Design and patients Thirty-two hyperthyroid Graves' disease patients (mean age 31 years) and 32 sex-, age-, and body mass index (BMI)-matched normal control subjects were recruited to receive one-channel electrocardiogram (ECG) recording.

**Measurements:**
The cardiac autonomic nervous function was evaluated by the spectral analysis of HRV, which indicates the autonomic modulation of the sinus node. The correlation coefficients between serum thyroid hormone concentrations and parameters of the spectral HRV analysis were also computed.

**Results:**
The hyperthyroid patients revealed significant differences (P < 0·001) compared with the controls in the following HRV parameters: a decrease in total power (TP), very low frequency power (VLF), low frequency power (LF), high frequency power (HF), and HF in normalized units (HF%); and an increase in LF in normalized units (LF%) and in the ratio of LF to HF (LF/HF). After correction of hyperthyroidism in 28 patients, all of the above parameters were restored to levels comparable to those of the controls. In addition, serum thyroid hormone concentrations showed significant correlations with spectral HRV parameters.

**Conclusions:**
Hyperthyroidism is in a sympathovagal imbalanced state, characterized by both increased sympathetic and decreased vagal modulation of the heart rate. These autonomic dysfunctions can be detected simultaneously by spectral analysis of HRV, and the spectral HRV parameters could reflect the disease severity in hyperthyroid patients.

29. The role of the autonomic nervous system in the resting tachycardia of human hyperthyroidism.

The mechanisms that control resting heart rate in hyperthyroidism were evaluated in six patients before and after treatment with propylthiouracil. The patients were subjected to pharmacological blockade under resting conditions in two experimental sessions: first session, propranolol (0.2 mg/kg body weight); second session, atropine (0.04 mg/kg body weight) followed by propranolol (0.2 mg/kg body weight). All drugs were administered intravenously. Resting heart rate was significantly reduced from 100 +/- 6.5 beats/min to 72 +/- 2.5 beats/min (P less than 0.005) after clinical and laboratory control of the disease. After double blockade, intrinsic heart rate was reduced from 105 +/- 6.8 beats/min before treatment to 98 +/- 6.0 beats/min after treatment (P less than 0.025). The reduction in heart rate caused by propranolol was not significantly different before (-13 +/- 1.4 beats/min) and after (-9 +/- 1.0 beats/min) propylthiouracil. In contrast, atropine induced a higher elevation of heart rate after treatment (45 +/- 8.6 beats/min) than before treatment (26 +/- 4.0 beats/min). The present results suggest no appreciable participation of the sympathetic component of the autonomic nervous system in the tachycardia of hyperthyroidism, at least under the conditions of the present study. The small change observed in intrinsic heart rate, although significant, seems to indicate that this is not the most important mechanism involved in this tachycardia. Our results suggest that an important reduction in the efferent activity of the parasympathetic component participates in the mechanisms that modify resting heart rate in hyperthyroidism.

30. Power spectral analysis of variations in heart rate in patients with hyperthyroidism or hypothyroidism.

Power spectral analysis (PSA) of the variation in heart rate is useful in determining the relative activity of the sympathetic and parasympathetic nerves. In this study, PSA was used to investigate the relationship
between abnormalities in autonomic nerve function and the presence of thyroid disorders in patients with autoimmune thyroid diseases. The low frequency (LF) or high frequency (HF) components of R-R variations were determined by PSA. The coefficient of variation of the R-R time intervals (CV(R-R)) was positively correlated with HF in healthy subjects. In untreated hyperthyroid patients with Graves' disease, the CV(R-R) and HF values were significantly lower than in healthy controls. Moreover, the LF/HF ratio in patients with untreated Graves' disease was significantly higher, and the LF/HF ratio in hypothyroid patients with Hashimoto's thyroiditis was significantly lower than in healthy controls. A negative correlation was observed between serum levels of free thyroid hormones (FT4 and FT3) and HF in Graves' disease patients. In some hyperthyroid patients, antithyroid drug therapy or beta-blocker administration gradually restored reduced HF values. Present results suggest that relative vagal nerve activity is reduced in hyperthyroid patients and that this reduction is reversible according to the decrease in serum levels of thyroid hormones.

31. Short-term variability of blood pressure and heart rate in hyperthyroidism

The effect of hyperthyroidism on the short-term memory variability of blood pressure and heart rate was evaluated in 12 untreated hyperthyroid patients during thyrotoxicosis and after a 6 1/2 month treatment designed to achieve a stable euthyroid state. Beat-by-beat finger blood pressure was measured with a Finapres device. The pulse interval, from which pulse rate was derived, was obtained from the blood pressure signal. Due to the significant change in heart rhythm associated with thyrotoxicosis, both pulse interval (taken as a surrogate of heart period) and pulse rate (taken as a surrogate of heart rate) were computed. Power spectral analysis showed a reduction in the overall heart period variability in the supine position in the hyperthyroid compared to the euthyroid state. This effect was observed in the low-frequency (0.005-0.068 Hz), mid-frequency (0.068-0.127 Hz) and high-frequency (respiratory) domains as well, with a significant reduction of the modulus of these bands of 31%, 35% and 47%, respectively. The heart rate spectral modulus also exhibited a reduction of the high-frequency component (31%) in the supine position in the hyperthyroid subjects. These changes in heart rhythmicity corroborate a vagal deficit in hyperthyroidism. In addition, blood pressure spectral power exhibited a significant deficit in the orthostatism-induced mid-frequency systolic blood pressure rise in the hyperthyroid state (64%) compared with the euthyroid state. This observation may reflect a reduced vascular sympathetic activation with standing. The resulting vasodilatation could well contribute to normalize blood pressure in thyrotoxicosis in which cardiac output is increased.

32. Sympathovagal imbalance in hyperthyroidism

We assessed sympathovagal balance in thyrotoxicosis. Fourteen patients with Graves' hyperthyroidism were studied before and after 7 days of treatment with propranolol (40 mg 3 times a day) and in the euthyroid state. Data were compared with those obtained in a group of age-, sex-, and weight-matched controls. Autonomic inputs to the heart were assessed by power spectral analysis of heart rate variability. Systemic exposure to sympathetic neurohormones was estimated on the basis of 24-h urinary catecholamine excretion. The spectral power in the high-frequency domain was considerably reduced in hyperthyroid patients, indicating diminished vagal inputs to the heart. Increased heart rate and midfrequency/high-frequency power ratio in the presence of reduced total spectral power and increased urinary catecholamine excretion strongly suggest enhanced sympathetic inputs in thyrotoxicosis. All abnormal features of autonomic balance were completely restored to normal in the euthyroid state. β-Adrenoceptor antagonism reduced heart rate in hyperthyroid patients but did not significantly affect heart rate variability or catecholamine excretion. This is in keeping with the concept of a joint disruption of sympathetic and vagal inputs to the heart underlying changes in heart rate variability. Thus thyrotoxicosis
is characterized by profound sympathovagal imbalance, brought about by increased sympathetic activity in the presence of diminished vagal tone.

33. Plasma catecholamine concentrations in hyperthyroidism and hypothyroidism

Using a modification of the fluorometric method of Anton and Sayre, we have measured the plasma epinephrine (E) and norepinephrine (NE) concentrations in patients with thyroid dysfunction. There was no significant difference in plasma E in hyperthyroid or hypothyroid subjects, the values being similar to those observed in normal subjects. There was a striking relationship between age and plasma NE in the euthyroid individuals (r = 0.685, p < 0.001, N = 41). Observed plasma NE concentrations were similar in control subjects (21.05 ± 1.6 ng/100 ml; mean ± SEM) and hyperthyroid patients (22.33 ± 2.0 ng/100 ml). However, plasma NE was significantly increased in hypothyroidism (35.46 ± 3.9 ng/100 ml; p < 0.01) and remained statistically different when the age factor was excluded (31.31 ± 2.67 ng/100 ml; p < 0.025). There was no correlation between plasma NE and serum thyroxine (T4), free thyroxine (FT4), or triiodothyronine (T3), in any of the three groups studied. These data indicate that hyperthyroidism is accompanied by normal plasma NE concentrations and that hypothyroidism is associated with significantly increased plasma NE concentrations, possibly in an attempt to compensate for the lack of thyroid hormones.

34. Frequency Domain Analysis of Heart Rate Variability and their Correlations in Diabetes

Diabetes mellitus (DM) is frequently characterized by autonomic nervous dysfunction. Analysis of heart rate variability (HRV) has become a popular noninvasive tool for assessing the activities of autonomic nervous system (ANS). In this paper, changes in ANS activity are quantified by means of frequency and time domain analysis of R-R interval variability. Electrocardiograms (ECG) of 16 patients suffering from DM and of 16 healthy volunteers were recorded. Frequency domain analysis of extracted normal to normal interval (NN interval) data indicates significant difference in very low frequency (VLF) power, low frequency (LF) power and high frequency (HF) power, between the DM patients and control group. Time domain measures, standard deviation of NN interval (SDNN), root mean square of successive NN interval differences (rMSSD), successive NN intervals differing more than 50 ms (NN50 Count), percentage value of NN50 count (pNN50), HRV triangular index and triangular interpolation of NN intervals (TINN) also show significant difference between the DM patients and control group.

35. Higher levels of inflammation factors and greater insulin resistance are independently associated with higher heart rate and lower heart rate variability in normoglycemic older individuals: the Cardiovascular Health Study.

Objectives:
To explore the relationship between (1) insulin resistance and inflammation factors with (2) higher heart rate (HR) and lower heart rate variability (HRV) in normoglycemic older adults.

Design
Cross-sectional population-based study.

Participants
Five hundred forty-five adults aged 65 and older with normoglycemia (fasting glucose <100 mg/dL) who participated in the Cardiovascular Health Study.

Measurements
Serum levels of three inflammation proteins (C-reactive protein (CRP), interleukin 6 (IL-6), and fibrinogen); insulin resistance, quantified according to the homeostasis assessment model (HOMA-IR); HR; and four representative measures of HRV (the standard deviation of normal beat to beat intervals (SDNN), the root mean square of successive differences (rMSSSD), very low frequency
power (VLF), and the low- to high-frequency power ratio (LF/HF)) derived from 24-hour Holter recordings.

**Results**

High CRP and IL-6 levels were associated with higher HR and lower SDNN and VLF after adjustment for multiple covariates, including HOMA-IR and clinical cardiovascular disease. High IL-6 was also associated with lower LF/HF. Significant univariate inverse relationships between HOMA-IR and HR and HRV were also found, but the strengths of these relationships were attenuated after adjustment for inflammation factors.

**Conclusion**

Increased levels of inflammation markers and HOMA-IR are associated with higher HR and lower HRV. These findings suggest that inflammation may contribute to the pathogenesis of cardiovascular autonomic decline in older adults.

36. Independent Determinants of Second Derivative of the Finger Photoplethysmogram among Various Cardiovascular Risk Factors in Middle-Aged Men

The second derivative of the finger photoplethysmogram (SDPTG) has been used as a non-invasive examination for arterial stiffness. The present study sought to elucidate independent determinants of the SDPTG among various cardiovascular risk factors in middle-aged Japanese men. The SDPTG was obtained from the cuticle of the left-hand forefinger in 973 male workers (mean age: 44±6 years) during a medical checkup at a company. The SDPTG indices (bla and -d/a) were calculated from the height of the wave components. Multiple logistic regression analyses revealed that the independent determinants of an increased bla (highest quartile of the bla) were age (odds ratio [OR]: 1.12 per 1-year increase, 95% confidence interval [CI]: 1.09-1.15), hypertension (OR: 1.65, 95% CI: 1.03-2.65), dyslipidemia (OR: 1.51, 95% CI: 1.09-2.09), impaired fasting glucose/diabetes mellitus (OR: 2.43, 95% CI: 1.16-5.07), and a lack of regular exercise (OR: 2.00, 95% CI: 1.29-3.08). Similarly, independent determinants of a decreased dia (lowest quartile of the d/a) were age (OR: 1.11 per 1-year increase, 95% CI: 1.08-1.14), hypertension (OR: 3.44, 95% CI: 2.20-5.38), and alcohol intake 6 or 7 days per week (OR: 2.70, 95% CI: 1.80-4.06). No independent association was observed between the SDPTG indices and blood leukocyte count or serum C-reactive protein levels. In conclusion, the SDPTG indices reflect arterial properties affected by several cardiovascular risk factors in middle-aged Japanese men. The association between inflammation and the SDPTG should be evaluated in further studies.

37. Multiple metabolic syndrome is associated with lower heart rate variability. The Atherosclerosis Risk in Communities Study

**Objective:**
To test at the population level whether people with multiple metabolic syndrome (MMS) disorders have reduced cardiac autonomic activity (CAA).

**Research Design and Methods**
We examined the association between the level of CAA and MMS disorders, at the degree of clustering and the segregate combination levels, using a random sample of 2,359 men and women aged 45-64 years from the biracial, population-based Atherosclerosis Risk in Communities (ARIC) Study. Supine resting 2-min beat-to-beat heart rate data were collected. High-frequency (HF) (0.15-0.35 Hz) and low-frequency (LF) (0.025-0.15 Hz) spectral powers, the ratio of LF to HF, and the SD of all normal R-R intervals (SDNN) were used as the conventional indices of heart rate variability (HRV) to measure CAA. The MMS disorders included hypertension, type 2 diabetes, and dyslipidemia.

**Results**
HRV indices were significantly lower in individuals with MMS disorders.
The multivariable adjusted mean HF was 0.85 (beat/min)² in subjects with all three MMS disorders, in contrast to 1.31 (beat/min)² in subjects without any MMS disorder. At the segregated combination level, the multivariable adjusted means +/- SEM of HF were 1.34 +/- 0.05, 1.16 +/- 0.05, 1.01 +/- 0.17, and 1.34 +/- 0.05 (beat/min)², respectively, for subjects without any MMS disorder, with hypertension only, with diabetes only, and with dyslipidemia only, and the means +/- SEM of HF were 0.93 +/- 0.04, 0.70 +/- 0.15, and 1.20 +/- 0.05 (beat/min)², respectively, for subjects with diabetes and hypertension, diabetes and dyslipidemia, and hypertension and dyslipidemia. An increase in fasting insulin of 1 SD was associated with 88% higher odds of having a lower HF. The pattern of associations was similar for LF and SDNN.

Conclusions: These findings suggest that MMS disorders adversely affect cardiac autonomic control and a reduced cardiac autonomic control may contribute to the increased risk of subsequent cardiovascular events in individuals who exhibit MMS disorders.

45. Deficit in response inhibition in children with attention deficit/hyperactivity disorder (ADHD): impact of motivation?
To date, neuropsychological and psycho-physiological studies have revealed inconsistent results regarding an executive or motivational deficit explaining the response inhibition deficit in children with attention deficit/hyperactivity disorder (ADHD). Research on differentiating neuropsychological processes in ADHD subtypes is still scarce. Therefore, the motivational impact on response inhibition among boys with ADHD was examined in this study. In the first study, 19 boys with ADHDcombined type (ADHD-C) and 19 age-matched healthy control subjects performed a modified Go/No-Go task with the following experimental conditions: neutral, auditory feedback, reward, response cost, and reward/response cost. Performance and physiological data (heart rate and skin conductance responses) were recorded. In a second study with the modified Go/No-Go task, data for six children with ADHD-C, six with ADHD-inattentive subtype (ADHD-I), and six healthy control subjects were compared. Neither of the two studies revealed group by condition interactions. In study 1, boys with ADHD-C generally made more commissions and omissions compared to the control group. However, feedback significantly improved the response inhibition in all children. The heart rate of all children was increased in the two conditions of reward and reward/response cost. Study 2 revealed that children with ADHD-I responded more slowly and showed increased reaction time variability compared to both other groups. The present study supports an executive rather than a motivational deficit in the response inhibition among children with ADHD-C, though further results also indicate the role of auditory feedback on response inhibition. Additionally, the findings support the differentiation of ADHD-C and ADHD-I, suggesting that ADHD-I children are characterized by a sluggish cognitive tempo.

67. Correlation between HOMA2 and HbA1c with algorithms derived from bioimpedance and spectrophotometric devices

Background
Homeostasis model assessment of insulin resistance (HOMA2-IR) and HbA1c, markers of metabolic syndrome and glycemic control, were compared with Electro Sensor (ES) Complex software algorithms. ES Complex software integrates data from Electro Sensor Oxi (ESO; spectrophotometry) and Electro Sensor-Body Composition (ES-BC; bioimpedance).

Methods
148 Brazilian obese candidates for bariatric surgery underwent complete physical examinations, laboratory tests (fasting plasma glucose, fasting plasma insulin and HbA1c) and ES Complex assessments. HOMA2-IR was calculated from fasting plasma glucose and fasting plasma insulin using
free software provided by The University of Oxford Diabetes Trial Unit. ES Complex–insulin resistance (ESC-IR) and ES Complex–blood glucose control (ESC-BCG) were calculated from ESO and ES-BC data using ES Complex software. Correlations between HOMA2-IR and ESC-IR and between ESC-BCG and HbA1c were determined.

Results
ESC-BCG was correlated with HbA1c \((r=0.85)\). ESC-BCG values \(>\)3 were predictive of HbA1c \(>\)6.5\% \((\varphi=0.94; \text{unweighted } \kappa=0.9383)\). ESC-IR was correlated with HOMA2-IR \((r=0.84)\). Patients with ESC-IR score \(>\)2.5 or \(>\)3, were more likely to have metabolic syndrome or insulin resistance, respectively, compared with HOMA2-IR value \(>\)1.4 and \(>\)1.8, respectively. ESC-IR performance was evaluated by ROC curves. The areas under the curve for metabolic syndrome and insulin resistance were 0.9413 and 0.9022, respectively.

Conclusion
The results of this study in Brazilian subjects with obesity suggest that ES Complex algorithms will be useful in large-scale screening studies to predict insulin resistance, metabolic syndrome and HbA1c >6.5\%. Additional studies are needed to confirm these correlations in non-obese subjects and in other ethnic groups.

68. Correlation between physiological data algorithms with the homeostasis model assessment (HOMA) and with blood glycated hemoglobin (HbA1c)

Background: The pathogenesis of type 2 diabetes is hypothesized to be related to two principal factors: insulin resistance and \(\beta\) cell function. Only blood tests and related algorithms are used to assess these factors. Physiologic data affected by these factors have never been used to screen for diabetes and prediabetes.

The aim of this study was to assess the correlation of algorithms from physiologic data with the HOMAIR and HOMA-\(\beta\) algorithms and HbA1C.

Methods: 148 patients (117 women and 31 men) mean age 39 (range 17–62) years were included in the study and were undergoing laboratory tests including fasting blood glucose, fasting insulin plasma, HbA1c and LDL Cholesterol, blood pressure measurement and examination with the E.S Complex system.

The ES Complex system is a combination of devices managed by software, and the data obtained from the system include tissue acid base balance, arterial stiffness, autonomic nervous system level activity and body composition.

The HOMA (Homeostasis model assessment) algorithms were calculated from the fasting blood glucose and the fasting insulin plasma (HOMA-IR and HOMA-\(\beta\)) and ESC algorithms were calculated from the E.S Complex data.(ESC-IR, ESC-\(\beta\) and ESC BGC).

Statistical analysis was conducted to determine the correlation between ESC-IR (ESC-Insulin Resistance) and HOMA-IR (HOMA-Insulin Resistance), correlation between the ESC-\(\beta\) (HS- \(\beta\) cell function) and HOMA-\(\beta\) (HOMA- \(\beta\) cell function) and correlation between the ESC-BCG (ESC-Blood Glucose Control) and HbA1c values.

Results:
The correlation between ESC-IR and HOMA-IR calculated with Spearman's coefficient of rank correlation \((\rho)=0.909\) and \(p<0.0001\) The correlation between ESC \(\beta\) and HOMA-\(\beta\) calculated with Spearman's coefficient of rank correlation \((\rho)=0.876\) and \(p<0.0001\)

The correlation between ESC BGC and HbA1c values calculated with Spearman's coefficient of rank correlation \((\rho)=0.786\) and \(p<0.0001\)

Conclusion:
The E S Complex algorithms have a very high correlation to the HOMA algorithms and blood glycated hemoglobin (HbA1c) and therefore predictive capacity to screen insulin resistance, \(\beta\) cell function and blood glucose control.
The ES Complex can be used as a rapid, cost-effective, and noninvasive tool in prediabetes and diabetes screening on a larger scale. The screening should be used to indicate the need for further evaluation – not as a basic for diagnosis.

69. Increased Fat Mass Compensates for Insulin Resistance in Abdominal Obesity and Type 2 Diabetes.

To evaluate the relative impact of abdominal obesity and newly diagnosed type 2 diabetes on insulin action in skeletal muscle and fat tissue, we studied 61 men with (n = 31) or without (n = 30) diabetes, subgrouped into abdominally obese or nonobese according to the waist circumference. Adipose tissue depots were quantified by magnetic resonance imaging, and regional glucose uptake was measured using 2-[18F] fluoro-2-deoxyglucose/positron emission tomography during euglycemic hyperinsulinemia. Across groups, glucose uptake per unit tissue weight was higher in visceral (20.5 ± 1.4 μmol · min⁻¹ · kg⁻¹) than in abdominal (9.8 ± 0.9 μmol min⁻¹ · kg⁻¹, P < 0.001) or femoral (12.3 ± 0.6 μmol · min⁻¹ · kg⁻¹, P < 0.001) subcutaneous tissue and ~40% lower than in skeletal muscle (33.1 ± 2.5 μmol · min⁻¹ · kg⁻¹, P < 0.0001). Abdominal obesity was associated with a marked reduction in glucose uptake per unit tissue weight in all fat depots and in skeletal muscle (P < 0.001 for all regions). Recent type 2 diabetes per se had little additional effect. In both intra-abdominal adipose (r = −0.73, P < 0.0001) and skeletal muscle (r = −0.53, P < 0.0001) tissue, glucose uptake was reciprocally related to intra-abdominal fat mass in a curvilinear fashion. When regional glucose uptake was multiplied by tissue mass, total glucose uptake per fat depot was similar irrespective of abdominal obesity or type 2 diabetes, and its contribution to wholebody glucose uptake increased by ~40% in obese nondiabetic and nonobese diabetic men and was doubled in obese diabetic subjects. We conclude that 1) in abdominal obesity, insulin-stimulated glucose uptake rate is markedly reduced in skeletal muscle and in all fat depots; 2) in target tissues, this reduction is reciprocally (and nonlinearly) related to the amount of intra-abdominal fat; 3) mild, recent diabetes adds little insulin resistance to that caused by abdominal obesity; and 4) despite fat insulin resistance, an expanded fat mass (especially subcutaneous) provides a sink for glucose, resulting in a compensatory attenuation of insulin resistance at the whole-body level in men.

70. Weight as a risk factor for clinical diabetes in women

To determine the relation of body mass index (weight/height²) with the risk of clinical non-insulindependent diabetes, the author’s analyzed data from a cohort of 113,861 US women aged 30–55 years in 1976. During 8 years of follow-up (826,010 person-years), 873 definite cases were identified among women initially free from diagnosed diabetes. Among women of average body mass index, 23–23.9 kg/m² the relative risk was 3.6 times that of women having a body mass index less than 22 kg/m² the risk continued to increase above this level of body mass index. The authors observed a much weaker positive association with weight at age 18, and this association was eliminated after adjustment for current body mass index. Thus, weight gain after age 18 was a major determinant of risk. For an increase of 20–35 kg, the relative risk was 11.3, and for an increase of more than 35 kg, the relative risk was 17.3. Adjusting for family history did not appreciably alter the strong relation observed among women at average levels of body mass index. These data indicate that, at even average weight, women are at increased risk of clinical non-insulin-dependent diabetes and that the relation between body mass index and risk of diabetes is continuous.

71. Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus

We examined the relationship between peripheral/hepatic insulin sensitivity and abdominal superficial/deep subcutaneous fat (SSF/DSF) and intra-abdominal visceral fat (VF) in patients with type 2 diabetes mellitus (T2DM). Sixty-two T2DM patients (36 males and 26 females, age = 55 +/- 3 yr, body
mass index = 30 +/- 1 kg/m2) underwent a two-step euglycemic insulin clamp (40 and 160 mU. m(-2). min(-1)) with [3-3H]glucose. SSF, DSF, and VF areas were quantitated with magnetic resonance imaging at the L(4-5) level. Basal endogenous glucose production (EGP), hepatic insulin resistance index (basal EGP x FPI), and total glucose disposal (TGD) during the first and second insulin clamp steps were similar in male and female subjects. VF (159 +/- 9 vs. 143 +/- 9 cm2) and DSF (199 +/- 14 vs. 200 +/- 15 cm2)) were not different in male and female subjects. SSF (104 +/- 8 vs. 223 +/- 15 cm2) was greater (P < 0.0001) in female vs. male subjects despite similar body mass index (31 +/- 1 vs. 30 +/- 1 kg/m2) and total body fat mass (31 +/- 2 vs. 33 +/- 2 kg). In male T2DM, TGD during the first insulin clamp step (1st TGD) correlated inversely with VF (r = -0.45, P < 0.01), DSF (r = -0.46, P < 0.01), and SSF (r = -0.39, P < 0.05). In males, VF (r = 0.37, P < 0.05), DSF (r = 0.49, P < 0.01), and SSF (r = 0.33, P < 0.05) were correlated positively with hepatic insulin resistance. In females, the first TGD (r = -0.45, P < 0.05) and hepatic insulin resistance (r = 0.49, P < 0.05) correlated with VF but not with DSF, SSF, or total subcutaneous fat area. We conclude that visceral adiposity is associated with both peripheral and hepatic insulin resistance, independent of gender, in T2DM. In male but not female T2DM, deep subcutaneous adipose tissue also is associated with peripheral and hepatic insulin resistance.

72. Insulin resistance and hypersecretion in obesity: European Group for the Study of Insulin Resistance (EGIR)

Insulin resistance and insulin hypersecretion are established features of obesity. Their prevalence, however, has only been inferred from plasma insulin concentrations. We measured insulin sensitivity (as the whole-body insulin-mediated glucose uptake) and fasting posthepatic insulin delivery rate (IDR) with the use of the euglycemic insulin clamp technique in a large group of obese subjects in the database of the European Group for the Study of Insulin Resistance (1,146 non-diabetic, normotensive Caucasian men and women aged 18-85 yr, with a body mass index (BMI) ranging from 15 to 55 kg.m-2). Insulin resistance, defined as the lowest decile of insulin sensitivity in the lean subgroup (608 subjects with a mean BMI of 29 kg.m-2). Insulin sensitivity declined linearly with BMI at an age- and sex-adjusted rate of 1.2 micromol.min-1.kg FFM-1 per BMI unit (95% confidence intervals = 1.0-1.4). Insulin hypersecretion, defined as the upper decile of IDR, was significantly (P<0.0001) more prevalent (38%) than insulin resistance in the obese group. In the whole dataset, IDR rose as a function of both BMI and insulin resistance in a nonlinear fashion. Neither the waist circumference nor the waist-to-hip ratio, indices of body fat distribution, was related to insulin sensitivity after adjustment for age, gender, and BMI; both, however, were positively associated (P<0.001) with insulin hypersecretion, particularly in women. In nondiabetic, normotensive obese subjects, the prevalence of insulin resistance is relatively low, and is exceeded by the prevalence of insulin hypersecretion, particularly in women with central obesity. In the obese with preserved insulin sensitivity, risk for diabetes, cardiovascular risk, and response to treatment may be different than in insulin resistant obesity.

73. New approach for large scale screening for the asymptomatic Hepatitis C Virus (HCV).

Background: Combination of technologies such as Bioimpedance and spectrophotometry has been shown to be a safe technique when used in a number of biomedical applications. The aim of this research was to assess the utility of combination of technologies as rapid, cost-effective, and noninvasive tools to detect asymptomatic chronic hepatitis C Virus in large scale.

It should be used to indicate the need for further evaluation – not as a basic for diagnosis. Methods: 91 patients were undergoing for lab tests including Anti-HCV test, and Liver Panel; ALT, AST, and for an examination E.S Complex (Electro Sensor Complex) system using a combination of technologies such as the Bioimpedance and the spectrophotometry. 41 patients (group 1) were found Anti HCV test positive and 50 patients were found negative (group 2). Statistical analysis was conducted between the 2 groups using receiver operating characteristic curves to
determine the specificity and sensitivity to detect C hepatitis with the ES Complex algorithm calculated from data such as the conductivity measurement and the arterial stiffness.

Results: The ES Complex algorithm using the stiffness index and delta for the conductivity value in the pathway right foot – left hand minus left hand-right foot had a sensitivity of 82.9 % and specificity of 84.8 % (cutoff > 201) and \( P = 0.0001 \).

Conclusion: The E.S Complex has a very high sensitivity and specificity, and it can be used at low cost and rapid screening and follow ups in large scale for asymptomatic hepatitis C virus.

74. Cardiac Autonomic Dysregulation in Patients with Acute Hepatitis

Background: Autonomic dysfunction is common in patients with chronic liver disease, but it is still unclear whether acute hepatitis coincides with alterations in autonomic functions.

Methods: We evaluated the heart rate variability (HRV) of 10 patients with acute hepatitis (6 males, 4 females; mean age, 44.0 y; range, 20-69 y). Frequency-domain analysis of short-term and stationary R-R intervals was performed on the first day of admission to detect low-frequency power (LF; 0.04-0.15 Hz), high-frequency power (HF, 0.15-0.40 Hz), the ratio of LF to HF (LF/HF), and LF in normalized units (LF%). The same measurement was repeated on the 7th day of admission.

Results: We found that there was a significant increase of HF as well as variance of the R-R interval on the 7th day after admission (\( P < 0.05 \)). There was a significant negative correlation between HF and the change of total bilirubin (\( P < 0.05 \)).

Conclusions: The study demonstrates a change in cardiac vagal tone associated with acute hepatitis by analysis of HRV, and such alteration is less pronounced later during the clinical course of acute hepatitis.

75. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium.

A prolongation of QT interval has been shown in patients with cirrhosis and it is considered as part of the definition of the so-called ‘cirrhotic cardiomyopathy’. The aim of the present study was to assess the determinants of QT interval prolongation in cirrhotic patients. Forty-eight male patients with different stages of liver disease were divided into three subgroups according to the Child–Pugh classification. All patients underwent a 24-h ECG Holter recording. The 24-h mean of QT intervals corrected for heart rate (termed QTc) and the slope of the regression line QT/RR were calculated.

HRV (heart rate variability), plasma calcium and potassium concentration and HVPG (hepatic venous pressure gradient) were measured. QTc was progressively prolonged from Child A to Child C patients (\( P=0.001 \)). A significant correlation between QTc and HVPG was found (\( P=0.003 \)). Patients with alcohol-related cirrhosis presented QTc prolongation more frequently than patients with post-viral cirrhosis (\( P<0.001 \)). The QT/RR slope was steeper in subjects with alcoholic aetiology as compared with viral aetiology (\( P=0.02 \)), suggesting that these patients have a further QTc prolongation when heart rate decreases. The plasma calcium concentration was inversely correlated with QTc (\( P<0.001 \)).

The presence of severe portal hypertension was associated with decreased HRV (\( P<0.001 \)). Cirrhotic patients with a more severe disease, especially of alcoholic aetiology, who have greater HVPG and lower calcium plasma levels, have an altered ventricular repolarization and a reduced vagal activity to the heart, which may predispose to life-threatening arrhythmias.

76. Chronic hepatitis C virus infection associated with autonomic dysfunction

Background: Impaired autonomic function has been described in patients with chronic liver diseases from different aetiologies, and has proven to be a poor prognostic indicator. To date, it is not known how chronic hepatitis C virus (HCV) infection affects the autonomic nervous system.

Aims: In the present study, we compared cardiovagal autonomic function in patients with chronic HCV infection and healthy controls and examined the relation between autonomic function and serum levels of
aminotransferases, HCV RNA, cryoglobulins, albumin and glucose.

Methods: Autonomic function was assessed in 45 treatment-naïve patients with chronic HCV infection and in 40 healthy controls by determining spontaneous baroreflex sensitivity (BRS) and heart rate variability (HRV) indices. The R–R interval was determined by electrocardiogram recording; continuous radial artery pressure was monitored simultaneously by applanation tonometry. Laboratory analyses and quantitative polymerase chain reaction for serum HCV RNA level were performed by standard procedures.

Results: BRS and HRV time and frequency domain indices were lower in patients with HCV infection compared with healthy controls [7.1±3.4 vs. 11.5±6.5 ms/mmHg for BRS, 168.5±160.9 vs. 370.7±349.4 ms² for low-frequency HRV (mean±SD); P<0.01]. Multivariate analysis showed that autonomic dysfunction in HCV-infected patients correlated with elevated alanine aminotransferase levels, but was not associated with serum HCV RNA levels and cryoglobulins.

Conclusion: Our results suggest that impaired autonomic function is caused by chronic HCV infection. Further studies are needed, however, to identify the underlying mechanisms.


Background: Bioimpedance is an electrical property of living tissue that has been shown to be a safe technique when used in a number of biomedical applications. The aim of this research was to assess the utility of bioimpedance measurement as a rapid, cost-effective, and noninvasive adjunct to digital rectal examination and PSA in differentiating tumor from normal prostatic tissue.

Methods: Three hundred men were examined for signs and symptoms of prostate disorders. 147 patients with a digital rectal examination indicating a positive result underwent a prostate-specific antigen (PSA) test. A biopsy was advised for 103 of the men, of whom 50 completed the study. Before undergoing biopsy, an examination with the EIS (electro interstitial scan) system using bioimpedance and chronoamperometry was performed. In reference to the biopsy results (negative or positive), a statistical analysis of the EIS data and PSA was conducted using receiver operating characteristic curves to determine the specificity and sensitivity of each test.

Results: The PSA test had a sensitivity of 73.9% and specificity of 51.9% using a cutoff value > 4 and a sensitivity of 52.2% and specificity of 81.5% using a cutoff value ≥ 5.7 and P = 0.03. The delta of the electrical conductivity (DE) of the left foot-right foot pathway had a sensitivity of 62.5% and specificity of 85.2%, with a cutoff value ≤ -5 and P = 0.0001. Algorithms comprising the delta of electrical conductivity and PSA showed a sensitivity of 91.5% and a specificity of 59.3%, with a cutoff value ≤ -10.52 and P = 0.0003.

Conclusion: The EIS system had a very good specificity of 85.2%. However, the sensitivity of 62.5% would be a problem. Using a PSA reference > 4.1 ng/mL, the adjunctive use of bioimpedance and chronoamperometry provided by EIS technology could raise the sensitivity from 73.9% to 91.5% and the specificity from 51.9% to 59.3% in prostate cancer screening.

78. Pediatrics New marker using the bioimpedance technology in Attention Deficit/Hyperactivity Disorder (ADHD) Children screening in adjunct to the conventional diagnostic methods.

Background: Diagnosis of ADHD children is not straightforward and misdiagnosis may, which leads to the dramatic possibility of error in treatments associated with numerous side effects which could be especially damaging in view of the age of the population. For this reason, a tool that is easy to use, fast and cost effective that could provide a new marker is warranted in adjunct to the conventional diagnosis and treatment monitoring of ADHD children. In this study we used a device named Electro Interstitial Scan (EIS) performing bioimpedance measurements and we compared the results of the conductivity measurements at the level of forehead electrodes between a group of children conventionally diagnosed with ADHD and a control group not showing any symptom of ADHD.
Method:
52 children were diagnosed ADHD following a psychiatric examination and 60 children without any symptom of ADHD underwent an examination with E.I.S (Electro Interstitial Scan) system.
2 groups were constituted:
Group 1: 60 Children assumed to be non ADHD children without any symptom of the and not undergoing any treatment. (Mean age 8.7 years old and 27 girls).
Group 2: 52 Children diagnosed to have ADHD from the psychiatric opinion according to the DSM-IV and further examinations and not undergoing any treatment. (Mean age 8 years old and 14 girls).
Statistical analysis was performed to compare the conductivity measurements at the level of the forehead electrodes using independent T-tests and receiver operating characteristic curve to determine the specificity and sensitivity of the test.

Results:
Independent sample T-test results:
The mean of the 2 pathways of the ADHD group was \( M=33.11\mu\text{Si} \) (from 2 to 113\( \mu\text{Si} \)) was significantly \((p<0.001)\) higher than the mean of the 2 pathways of the control group \( M=2.75\mu\text{Si} \) (from 1.75 to 27.4\( \mu\text{Si} \)).

Receiver operating characteristic curve results:
The parameter mean of conductivity of the pathway between the forehead electrodes has a specificity of 98% and sensitivity of 80 % and \( p=0.0001 \) (Upper 95% CI) using a cutoff value at 7.4 \( \mu\text{Si} \).

Conclusion
The EIS marker related to the conductivity measurement of the forehead pathway has a high specificity and high sensitivity and use of this could provide practitioners with a non-invasive, low-cost system, that is easy to use in the office, and that could offer an adjunct in the conventional diagnosis of ADHD children and also in treatment monitoring, and, from this result, provide earlier intervention.

79. Heart rate and reinforcement sensitivity in ADHD.

Background
Both theoretical and clinical accounts of attention-deficit/hyperactivity disorder (ADHD) implicate a dysfunctional reinforcement system. This study investigated heart rate parameters in response to feedback associated with reward and response cost in ADHD children and controls aged 8 to 12.

Methods
Heart rate responses (HRRs) following feedback and heart rate variability (HRV) in the low frequency band (0.04-0.08 Hz), a measure of mental effort, were calculated during a time production paradigm. Performance was coupled to monetary gain, loss or feedback-only in a crossover design.

Results
Children with ADHD exhibited smaller HRRs to feedback compared to controls. HRV of children with ADHD decreased when performance was coupled to reward or response cost compared to feedback-only. HRV of controls was similar across conditions.

Conclusions
Children with ADHD were characterized by (a) possible abnormalit

80. Heart Rate Variability and Sustained Attention in ADHD Children.
The major goal of the current study was to investigate the association between continuous performance tests (CPTs) and the heart rate variability (HRV) of attention deficit hyperactivity disorder (ADHD) children. The HRV, specifically the 0.10-Hz component, may be considered to be a psycho physiological index of effort allocation (motivation): The less effort the subject allocates, the greater the 0.10-Hz component. Results indicated that, compared to controls, ADHD subjects had a
greater 0.10-Hz component, which was associated with poor test performance over time. Thus, using a psycho physiological measure, we were able to confirm the clinical concept of ADHD from a motivational perspective.

81. Changes in the cardiac autonomic regulation in children with attention deficit hyperactivity disorder.

Background & objectives: ADHD is one of the most common mental disorders among children. We hypothesized that ADHD is associated with the impairment of the cardiac autonomic regulation. The aim of this study was to evaluate the cardiac autonomic regulation in children with ADHD at the rest and during orthostasis using short-term heart rate variability (HRV) analysis.

Methods: Eighteen children with ADHD admitted to the Department of Children and Adolescent Psychiatry, Clinic of Psychiatry, University Hospital in Martin, Slovak Republic between January and September 2006 and 18 matched healthy subjects were recruited. HRV analysis was carried out in three positions: supine (S1)-orthostasis (O)-supine (S2). Evaluated parameters were: the mean R-R interval, mean squared successive difference (MSSD), spectral powers in low (LF) and high frequency (HF) bands, total power (TP), coefficients of component variance (CCV LF, CCV HF), LF/HF ratio.

Results: The mean R-R interval was significantly shorter in ADHD group compared to controls in all positions (P<0.05, P<0.001). S1: The parameters MSSD, CCV HF, log HF power were significantly lower (P<0.05, P<0.05, P<0.01) and ratio LF/HF was significantly higher (P<0.05) in ADHD group compared to controls. O: The parameters MSSD, CCVHF, log HF power, log TP were significantly lower in ADHD group compared to controls (P<0.01, P<0.05,P<0.01, P<0.01). S2: The parameters MSSD and log HF power were significantly lower in children with ADHD compared to controls (P<0.05).

Interpretation and conclusions: The children with ADHD had decreased cardiac vagal modulation and tachycardia in supine positions with altered ability of dynamic activation of the autonomic nervous system in response to orthostasis indicating changes in the cardiac autonomic regulation. Further studies need to be done on a larger sample to confirm these findings and to understand the underlying mechanisms.

83. Vasoactive Agents and Vascular Aging by the Second Derivative of Photoplethysmogram Waveform

Assessment of Hypertension: Volume 32(2)August 1998pp 365-370

To evaluate the clinical application of the second derivative of the fingertip photoplethysmogram waveform, we performed drug administration studies (study 1) and epidemiological studies (study 2). In study 1, ascending aortic pressure was recorded simultaneously with the fingertip photoplethysmogram and its second derivative in 39 patients with a mean +/- SD age of 54 +/- 11 the early systolic peak in the pulse. The second derivative consists of an a, b, c, and d wave in systole and an e wave in diastole. Ascending aortic pressure increased after injection of 2.5 [micro sign]g angiotensin from 126/74 to 160/91 mm Hg and decreased after 0.3 mg sublingual nitroglycerin to 111/73 mm Hg. The d/a, the ratio of the height of the d wave to that of the a wave, decreased after angiotensin from -0.40 +/- 0.13 to -0.62 +/- 0.19 and increased after nitroglycerin to -0.25 +/- 0.12 (P<0.001 and P<0.001, respectively). The negative d/a increased with increases in plethysmographic and ascending aortic augmentation indices (r=0.79, P<0.001, and r=0.80, P<0.001, respectively). The negative d/a reflects the late systolic pressure augmentation in the ascending aorta and may be useful for noninvasive evaluation of the effects of vasoactive agents. In study 2, the second derivative of the
plethysmogram waveform was measured in a total of 600 subjects (50 men and 50 women in each decade from the 3rd to the 8th) in our health assessment center. The b/a ratio increased with age, and c/a, d/a, and e/a ratios decreased with age. Thus, the second derivative aging index was defined as bc-d-e/a. The second derivative wave aging index (y) increased with age (x) \( r=0.80, P<0.001, y=0.023x-1.515 \). The second derivative aging index was higher in 126 subjects with any history of diabetes mellitus, hypertension, hypercholesterolemia, and ischemic heart disease than inagematched subjects without such a history (-0.06 +/- 0.36 versus -0.22 +/- 0.41, P<0.01). Women had a higher aging index than men (P<0.01). The b-c-d-e/a ratio may be useful for evaluation of vascular aging and for screening of arteriosclerotic disease. (Hypertension. 1998;32:365-370.)(C) 1998 American Heart Association, Inc.

85. Utility of Second Derivative of the Finger Photoplethysmogram for the Estimation of the Risk of Coronary Heart Disease in the General Population

Background Increased arterial stiffness has been shown to be associated with coronary heart disease (CHD). However, it remains unclear as to whether the second derivative of the finger photoplethysmogram (SDPTG), a non-invasive method for the assessment of arterial stiffness, is useful for the estimation of risk of CHD in the general population. Methods and Results The SDPTG in 211 subjects (age: 63±15 years, range: 21-91 years, 93 males) was recorded without apparent atherosclerotic disorders from a community. The relationship between the SDPTG indices (b/a and d/a) and coronary risk factors (n=211) or the Framingham risk score (n=158, age: 60±12 years, range: 30-74 years, 63 males) were analyzed. The SDPTG indices significantly correlated with the Framingham risk score in both genders (b/a; r\text{male} =0.43, r\text{female} =0.54 and d/a; r\text{male} =-0.38, r\text{female} =-0.58), as well as several coronary risk factors. In the receiver operating characteristics curve analyses, the b/a discriminated high-risk subjects for CHD, who were in the highest quintile of the Framingham risk score in each gender, with a sensitivity and specificity of 0.85 and 0.58 in males and 0.83 and 0.72 in females, respectively.

Conclusions. These results suggest that the SDPTG is useful for the estimation of risk of CHD in the general population. (Circ J 2006; 70: 304 - 310).

86. Noninvasive Determination of Age-Related Changes in the Human Arterial Pulse

Arterial pressure waves were recorded noninvasively from the carotid, radial, femoral, or all three of these arteries of 1,005 normal subjects, aged 2-91 years, using a new transcutaneous tonometer containing a high fidelity Millar micromanometer. Waves were ensemble-averaged into age-decade groups. Characteristic changes were noted with increasing age. In all sites, pulse amplitude increased with advancing age (carotid, 91.3%; radial 67.5%; femoral, 50.1% from first to eighth decade), diastolic decay steepened, and diastolic waves became less prominent. In the carotid pulse, there was, in youth, a second peak on the downstroke of the waves in late systole. After the third decade, this second peak rose with age to merge with and dominate the initial rise. In the radial pulse, a late systolic wave was also apparent, but this occurred later; with age, this second peak rose but not above the initial rise in early systole, even at the eighth decade. In the femoral artery, there was a single systolic wave at all ages. Aging changes in the arterial pulse are explicable on the basis of both an increase in arterial stiffness with increased pulse-wave velocity and progressively earlier wave reflection. These two factors may be separated and effects of the latter measured from pressure wavecontour analysis using an "augmentation index," determined by a computer algorithm developed from invasive pressure and flow data. Changes in peak pressure in the central (carotid) artery show increasing cardiac afterload with increasing age in a normal population; this can account for the cardiac hypertrophy that occurs with advancing age (even as other organs atrophy) and the predisposition to cardiac failure in the elderly. Identification of mechanisms responsible offers a new
approach to reduction of left ventricular afterload. (Circulation 1989;80:1652-1659).

87. Excess accumulation of body fat is related to dyslipidemia in normalweight subjects

Objective
To assess the relationship of fat mass (FM) and its distribution to hypertension and dyslipidemia in normal-weight Japanese individuals.

Design
Cross-sectional study.

Subjects:
Apparently healthy Japanese subjects with a body mass index (BMI) between 20 and 23.5 kg/m2 (265 males and 741 females, age 21–69 y).

Measurements:
BMI, waist circumference (WC), waist-hip ratio (WHR), systolic and diastolic blood pressure, serum levels of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C) and triglyceride (TG) were measured. Low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedewald formula. Percentage fat mass (%FM) and trunk fat mass–leg fat mass ratio (FMtrunk/FMlegs) were obtained by dual-energy X-ray absorptiometry.

Results:
WC, WHR, %FM and FMtrunk/FMlegs were significantly correlated with TC, LDL-C, HDL-C and TG with the tendency of FMtrunk/FMlegs to show the strongest correlations. For %FM and FMtrunk/FMlegs in both sexes, odds ratios (ORs) of the third tertiles with respect to the first tertiles increased for LDL-C elevation, TG elevation and dyslipidemia. In males, ORs of the third tertiles of WC were significantly high for LDL-C elevation and dyslipidemia whereas those of WHR were high for TG elevation and dyslipidemia. ORs of the third tertiles of WC and WHR were significantly high for TG elevation in females. BMI was not associated with the risk of abnormal lipid levels. ORs for hypertension showed significant increases in none of the variables of obesity.

Conclusions:
Excess accumulation of FM, especially to the upper body, was related to dyslipidemia in normal-weight subjects. Simple anthropometric variables, WC and WHR, may be useful for screening and management of dyslipidemia in these subjects.

88. The influence of the peripheral reflection wave on left ventricular hypertrophy in patients with essential hypertension.

The objective of this study was to clarify the relationship between afterload, which consists mainly of the vascular reflection wave, and left ventricular hypertrophy in patients with untreated essential hypertension using the fingertip photoplethysmogram (PTG) and second derivative wave (SDPTG) methods, the simplest and most convenient tools for pulse wave analysis. The augmentation index (AI) is defined as the ratio of the height of the late systolic peak, augmented by the peripheral reflection wave, to that of the early systolic peak caused mainly by left ventricular ejection in the pulse. Increased AI of the PTG and negative d/a, obtained by multiplying the ratio of the late redrecreasing wave (d wave) to the initial positive wave (a wave) of the SDPTG by -1, have the same meaning as increased ascending aortic AI. The left brachial artery blood pressure was measured in 60 patients. The PTG and SDPTG of the right second finger were recorded by a digital photoplethysmograph. The left ventricular mass index (LVMI) was investigated by ultrasonography. Subjects were assigned to one of two groups: a low AI (AI of PTG<1.6; group 1) or a high AI (AI of PTG> or =1.6; group 2) group. LVMI was significantly higher in group 2 than in group 1. In the study group as a whole, the LVMI was positively correlated with both the AI of PTG (r=0.60,
p<0.0001) and negative d/a (r=0.63, p<0.0001). An increase in the LVMI was seen in subjects with an augmented late systolic component in the waveform. It was concluded that an increase in the peripheral reflection wave on the left ventricle is one of the important factors causing cardiac hypertrophy in patients with hypertension.

89. Aortic Stiffness Is an Independent Predictor of Primary Coronary Events in Hypertensive Patients. A Longitudinal Study.

Arterial stiffness may predict coronary heart disease beyond classic risk factors. In a longitudinal study, we assessed the predictive value of arterial stiffness on coronary heart disease in patients with essential hypertension and without known clinical cardiovascular disease. Aortic stiffness was determined from carotid-femoral pulse wave velocity at baseline in 1045 hypertensives. The risk assessment of coronary heart disease was made by calculating the Framingham risk score according to the categories of gender, age, blood pressure, cholesterol, diabetes, and smoking. Mean age at entry was 51 years, and mean follow-up was 5.7 years. Coronary events (fatal and nonfatal myocardial infarction, coronary revascularization, and angina pectoris) and all cardiovascular events served as outcome variables in Cox proportional-hazard regression models. Fifty-three coronary events and 97 total cardiovascular events occurred. In univariate analysis, the relative risk of follow-up coronary event or any cardiovascular event increased with increasing level of pulse wave velocity; for 1 SD, ie, 3.5 m/s, relatives risks were 1.42 (95% confidence interval [CI], 1.10 to 1.82; P<0.01) and 1.41 (95% CI, 1.17 to 1.70; P<0.001), respectively. Framingham score significantly predicted the occurrence of coronary and all cardiovascular events in this population (P<0.01 and P<0.0001, respectively). In multivariate analysis, pulse wave velocity remained significantly associated with the occurrence of coronary event after adjustment either of Framingham score (for 3.5 m/s: relative risk, 1.34; 95% CI, 1.01 to 1.79; P=0.039) or classic risk factors (for 3.5 m/s: relative risk, 1.39; 95% CI, 1.08 to 1.79; P=0.01). Parallel results were observed for all cardiovascular events. This study provides the first direct evidence in a longitudinal study that aortic stiffness is an independent predictor of primary coronary events in patients with essential hypertension.


Current methods for assessing vasomotor endothelial function are impractical for use in large studies. We tested the hypothesis that pulse-wave analysis (PWA) combined with provocative pharmacological testing might provide an alternative method. Radial artery waveforms were recorded and augmentation index (AIx) was calculated from derived aortic waveforms. Thirteen subjects received sublingual nitroglycerin (NTG), inhaled albuterol, or placebo. Twelve subjects received NTG, albuterol, and placebo separately during an infusion of NG-monomethyl-L-arginine (LNMMA) or norepinephrine. Twenty-seven hypercholesterolemic subjects and 27 controls received NTG followed by albuterol. Endothelial function was assessed by PWA and forearm blood flow in 27 subjects. Albuterol and NTG both significantly and repeatably reduced AIx (P<0.001). Only the response to albuterol was inhibited by LNMMA (-9.8±5.5% vs -4.7±2.7%; P=0.02). Baseline AIx was higher in the hypercholesterolemic subjects, who exhibited a reduced response to albuterol (P=0.02) but not to NTG when compared with matched controls. The responses to albuterol and acetylcholine were correlated (r=0.5, P=0.02). Consistent with an endotheliumdependent effect, the response to albuterol was substantially inhibited by LNMMA. Importantly, the response to albuterol was reduced in subjects with hypercholesterolemia and was correlated to that of intra-arterial acetylcholine. This methodology provides a simple, repeatable, noninvasive means of assessing endothelial function in vivo.
91. Aortic stiffness as a risk factor for recurrent acute coronary events in patients with ischemic heart disease.

Background Aortic elastic properties, important determinants of left ventricular function and coronary blood flow, are compromised in hypertension. The aim of this study was to determine aortic function in hypertensive patients and in normal subjects before and after administration of diltiazem, a calcium antagonist widely used in the treatment of essential hypertension.

Methods and Results The aortic pressure-diameter relation was obtained before and after diltiazem administration in 15 hypertensives and 15 control normotensives. Instantaneous diameter of the thoracic aorta was acquired with a high-fidelity intravascular catheter developed in our institution and previously validated. Instantaneous aortic pressure was measured simultaneously and at the same aortic level with a catheter-tip micromanometer. Energy loss due to the viscosity of aortic wall was measured from the area of the loop. Aortic distensibility was calculated using the formula 2x(pulsatile change in aortic diameter)/[(diastolic aortic diameter)x[aortic pulse pressure]]. At baseline, aortic distensibility was lower and energy loss was greater in hypertensives than in normotensives (distensibility: 1.4±0.3 versus 3.5±0.7 cm² · dyne-1 · 10⁻⁶, respectively, P<.001; energy loss: 14.1±3.3 versus 8.2±2.2 mm · mm Hg, respectively, P<.001). After diltiazem administration, aortic distensibility was increased, whereas energy loss was decreased in both hypertensives (peak response: distensibility, 2.0±0.4 cm² · dyne-1 · 10⁻⁶, P<.001; energy loss, 9.3±1.6 mm · mm Hg, P<.001) and normotensives (peak response: distensibility, 5.2±0.5 cm² · dyne-1 · 10⁻⁶, P<.001; energy loss, 5.0±1.2 mm · mm Hg, P<.001).

Electro interstitial scan system: assessment of 10 years of research and development

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Abstract – Background

Ten years of research and development have allowed an understanding of how the electro interstitial scan (EIS) works and what its clinical applications may be.

Materials and methods

The EIS is a galvanic skin response device. The measurements are performed by electrical stimulation of the post sympathetic cholinergic fiber with weak DC current and voltage 1.28V applied during 2 minutes and in bipolar mode.

Current scientific knowledge

EIS electrical measurements are related to: (1) the concentration of free chloride ions in the interstitial fluid, which affects the transfer of electrical current and the ratio intensity/voltage; (2) the morphology of the interstitial fluid, which is related to the electrical dispersion calculated from the Cole equation (α parameter); (3) electrical stimulation, which causes a change in sweat rate at the passive electrodes – post sympathetic cholinergic fiber electrical stimulation appears to be responsible for activating M2 receptors, which regulate nitric oxide (NO) production in the endothelial cell and cause vasodilation and a released sweat response; and (4) the electrochemical redox reactions (electrolysis) of the released sweat on electrodes, which are different on the bulk of the metal electrodes (O2 + [4H+] + [4e−]) and on the Ag/AgCl disposable electrodes (AgCl precipitation).

Results

For each of the EIS clinical results, various explanations were posited, such as: (1) electrical stimulation of the postsympathetic cholinergic fiber-activating NO production in the endothelial cell, which causes vasodilation and a released sweat response (diabetes detection); (2) estimation of interstitial fluid’s acid–base balance, which is reflected in an electrochemical reaction on the bulk of the electrodes through the released sweat (prostate cancer detection); (3) estimation of cerebral interstitial fluid chloride ions (detection of ADHD in children); and (4) estimation of the morphology of the interstitial fluid (selective serotonin reuptake inhibitor treatment response).

Conclusion

After 10 years of development, the analysis of current scientific knowledge and results of clinical investigations have allowed a better understanding of EIS electrical measurements.

Keywords: EIS, electro interstitial scan, electrochemical redox reactions, postsympathetic cholinergic electrical stimulation, ADHD, SSRI treatment responses, prostate cancer, diabetes.

Introduction

Galvanic skin response (GRS) is a method of measuring the electrical conductance of the skin related to the sweat gland responses. The sweat glands are controlled by the post sympathetic cholinergic system. Thus, skin conductance has been used as an indication of psychological or physiological arousal. The first device used to measure the electrical conductance between two electrodes, was essentially a type of ohmmeter.

The scientific study of GSR began in the early 1900s. Reich studied GSR at the Psychological Institute at the University of Oslo in 1935, and confirmed the existence of a bio-electrical charge behind his concept of vegetative pleasurable streaming. GSR was used for a variety of research in the 1960s and 1970s,
with a decline in use as more sophisticated techniques (such as EEG and MRI) replaced it in many areas of psychological research. The EIS is classified as GSR, but unlike the ohmmeter, it was designed using a scientific basis including the electrochemistry, bioimpedance, and physiology of the sweat glands, with the objective being to produce reproducible measurements of conductance for use as markers of disease or indicators of treatment response. Also, EIS data are able to be sent to a computer for signal processing, analysis, and follow-up.

Ten years of development and clinical investigations have led to an understanding of how EIS works and what its clinical applications may be. In this paper, we present the results of this work including interpretation of conductance measurements and a discussion of clinical investigations.

Materials and methods

The EIS (Electro Interstitial Scan, LD Technology, Miami, FL) system includes a USB “plug and play” hardware device, an interface box, and six tactile electrodes and cables. The six electrodes are placed on the skin with two on the forehead (one on the left, one on the right), two in contact with the palms of the hands, and two in contact with the soles of the feet. The electrodes on the hands and feet are at least 250 cm² and are made of stainless steel. The forehead electrodes are disposable (single use), are 15.75 cm², and are made of Ag/AgCl. Software is installed on the computer, and the USB port provides data transfer as well as power to the hardware.

Contraindications

- Dermatological lesions in contact with the electrodes
- Excessive perspiration (hyperhidrosis)
- The patient using a cardiac pacemaker, being connected to electronic life support devices or any implanted electronic device, or the presence of defibrillators
- Patients who are unable to sit
- Metal pins or prostheses on the extremities or joints
- Pregnancy
- The absence of one or more limbs.

Description of the test procedure

The device and accessories are cleaned/disinfected and then dried in the air. This must be performed before each patient.

The examination area should be comfortable, free of portable electric heaters, and not drafty.

The measurement is carried out with the patient in a seated position.

The patient is barefoot and removes all metal objects (wristwatch, bracelets, rings, etc) which may come into contact with the electrodes.

Any creams, makeup, or foundation on the forehead are removed by wiping with alcohol, and then letting the area air dry.

The feet and hands are cleaned with alcohol, and then air-dried.

The patient must register and provide details including date of birth, weight, and height.

Measurement process

Automatic testing before measurement indicates that the hardware and software are operating correctly, and that the connection to the patient is acceptable. Once the EIS begins, a sequence of successive measurements is performed on eleven pathways of the body using weak DC current (200 μA) and an imposed voltage of 1.28 V between the six tactile electrodes (Table 1). The software changes the polarity for each pathway, first from anode to cathode and then from cathode to anode. The conductance of each pathway is measured every 32 milliseconds for 1 second for each polarity.
Table 1
Sequence of measurement of the 11 pathways
Description of the measurement process
The DC current circuit is shown in Figure 1 (steps of the current transfer from active electrode to passive electrode).

Figure 1
Steps of the current transfer from anode to cathode and then from cathode to anode for each pathway. Steps 1 and 2: entrance of the current from the active electrode
Because voltage lower than 10 V cannot penetrate the stratum corneum, the only way for the current to enter the body is through the eccrine sweat ducts. This route represents the physiological pathway of the interstitial fluid, i.e., the source of the eccrine sweat.4
Step 3: pathway into the human body between the two electrodes
According to Fricke’s circuit, the plasma membrane acts as an insulator and a DC current is not able to penetrate the cell, so most of the current flows around the cell through the interstitial fluid.5,6
In the interstitial fluid, free ions are able to conduct a current in the presence of an external electrical field. We can consider biological tissue to be an ionic conductor, both electrically and macroscopically. The total ionic conductance of a solution depends on the concentration, activity, charge, and mobility of all free ions in the solution.5,6
The ionic concentration is proportional to the ratio intensity/voltage, so that as the ionic concentration increases, more intensity and less voltage are observed.5,6
Electrical dispersion: The cell membrane has the ability to store capacitive energy (that is, it has dielectric or insulator properties). The cell membrane is the cellular structure that makes the largest contribution to the dielectric behavior of living tissue. Living tissue is considered to be a dispersive medium.7–9
In 1940, Cole introduced the first mathematical expression able to describe the “depressed semicircles” found experimentally. This is known as the Cole equation.\(^7\)–\(^9\)
\[
Z = R_\infty + \Delta R_1 + (j\omega\tau)\alpha, \quad \Delta R = R_0 - R_\infty
\]
where \(Z\) is the impedance value at frequency \(\omega\), \(j\) is the complex number \((-1)^{1/2}\), \(R_\infty\) is the impedance at infinite frequency, \(R_0\) is the impedance at zero frequency, \(\tau\) is the characteristic time constant, and \(\alpha\) is a dimensionless parameter with a value between 0 and 1. The \(\alpha\) value can also be regarded as a parameter denoting the derivation from the Fricke–Morse model. That is, the Cole equation with \(\alpha = 1\) is equal to the Fricke–Morse model.\(^10\)

In the case of living tissues, the spectral width of the electrical bioimpedance dispersions (closely related to the \(\alpha\) parameter in the Cole equation) evolves during the ischemic periods. Simulations indicate that the dispersion width could be determined by the morphology of extracellular spaces.\(^11\)

Steps 4, 5, and 6: Process of the exit of the current to the passive electrode

Electrical stimulation causes a released sweat response response.\(^12\) Mechanical shear stress causes a phosphorylation cascade that removes phosphate groups from proteins and kinases, activating endothelial NO synthase. NO is produced, facilitating the release of cyclic guanosine monophosphate, and a change in potassium permeability. The relaxation of the smooth muscle and vasodilatation of the vessels allows an exchange between vessels and the sweat glands, which facilitates the production of sweat.\(^12\),\(^13\)

Step 7: Electrochemical reactions on the bulk of the passive electrode (electrolysis)

Analysis of the DC current in the cathode and anode in electrolytic solution Na\(^+\)Cl\(^–\) using metal electrodes; the electrochemical window is defined by both reduction and oxidation of water according to the following reactions.\(^14\)

At the cathode

Na\(^+\) ions are not discharged at the cathode as sodium is not very electropositive, which means that it takes a lot of energy and a large negative voltage on the cathode to impose electrons on Na\(^+\) ions. At a lower voltage, dissolved oxygen is reduced and water molecules are decomposed. Both processes are linked with non-charged species that are transported to the electron transfer sites by diffusion rather than by migration.

When the voltage supply is adjusted (>1 V), oxygen reduction is performed. Na\(^+\) ions are necessary for the conductance of the solution.

The water electrochemical reaction (reduction) at the cathode is \(2\text{H}_2\text{O} + (2\text{e}–) = \text{(H}_2\text{)} + (2\text{OH}–)\).

At the anode

The current at the anode is due to the discharge of Cl\(^–\) ions. Chloride is highly electropositive, and less energy is necessary for taking electrons from the chloride ions than from water molecules. The water electrochemical reaction (oxidation) at the anode is \(2\text{H}_2\text{O} = (\text{O}_2) + (4\text{H}+) + (4\text{e}–)\).

In the interstitial fluid, Na\(^+\) represents 96% of the positive free ions, and Cl\(^–\) and HCO3\(^–\) ions represent 96% of the negative free ions.\(^14\)

The interstitial fluid can be considered an electrolytic solution of Na\(^+\) and Cl\(^–\) because HCO3\(^–\) and Na\(^+\) ions may not be discharged and they do not contribute very much to the DC current transfer.\(^3\) The in vitro electrochemical model described above can be applied only for the Cl\(^–\) ions at the anode.\(^14\)

Analysis of the DC current in anode in electrolytic solution Na\(^+\)Cl\(^–\) using Ag/AgCl

The Cotlove coulometric chloride titrator method measures the total chloride concentration.\(^15\) With this method, the passage of a constant direct current between Ag/AgCl electrodes produces silver ions. The free silver ions at the anode react with the chloride forming silver chloride as follows:

\[
\text{Ag} \rightarrow \text{Ag} + \text{Ag} + +(\text{Cl} – ) \rightarrow \text{AgCl}
\]

After all the chloride has combined with Ag\(^+\), free silver ions accumulate and precipitate, causing an increase in current across the electrodes and indicating the end point of the reaction. The technique is already used in vitro to assess the Cl\(^–\) concentration in small quantities of sweat.
**Results**

Cycle of measurements

The full cycle comprises 22 conductance measurements of the 11 pathways measured in the polarity anode-cathode in 1 second, and in the polarity cathode–anode (also in 1 second). The measurements’ values are displayed in a scale from 0 to 100 for each pathway and a fast Fourier transform graph at three frequencies (Figure 2).

![Figure 2](image)

Figure 2

Results of a cycle of measurements in numeric values and fast Fourier transform graph at three frequencies.

Signal processing analysis

The following results were analyzed for each segment/pathway:

- Conductance in $\mu$S of each anode–cathode pathway ($SDC_+)$
- Conductance in $\mu$S of each cathode–anode pathway ($SDC_-)$
- Numeric value in CU (conventional unit) ($delta SDC_+/SDC_-)$
- Dispersion of each pathway in CU (calculated using the Cole equation) ($\alpha$ parameter)
- Frequency or spectral analysis of the entire cycle of measurements
- Application of the fast Fourier transform (FFT) to the entire signal

The FFT includes EIS HF (high frequencies from 0.1875 to 0.50 Hz), EIS LF (low frequencies from 0.05 to 0.1875 Hz), and EIS VLF (very low frequencies from 0 to 0.05 Hz).

EIS reproducibility

Electrical stimulation caused an almost linear increase of sweat output after stimulation. Thereafter, sweat output decreased exponentially to baseline levels within 2 minutes. Repetitive electrical stimulation at 2.75-minute intervals reliably evoked a sweat response. No significant difference in sweat output was obtained between the three stimulations performed within each session.

EIS clinical investigations

Statistical analysis has been performed in 600 healthy subjects to determine the normal range of EIS conductance for each pathway. The results of EIS research have been published in peer-reviewed journals and show interesting clinical applications.

Improvement of the total PSA value in screening of prostate cancer

This research showed that the PSA test had a sensitivity of 73.9% and specificity of 51.9% using a cutoff value of 0.4 and a sensitivity of 52.2% and specificity of 81.5% using a cutoff value of 5.7 ($P = 0.03$). The delta of the electrical conductance (DE) of the left foot–right foot pathway had a sensitivity of 62.5% and specificity of 85.2%, with a cutoff value of $-5$ ($P = 0.0001$). Algorithms comprising the delta of electrical conductance and PSA showed a sensitivity of 91.5% and a specificity of 59.3%, with a cutoff value of $-10.52$ ($P = 0.0003$).

Measurable markers of the response of SSRI treatment

Fifty-nine subjects (mean age 47 years, range 17–76 years; 38 women) diagnosed with major depression disorder by psychiatric assessment at the Botkin Hospital according to DSM-IV and CGI (Clinical Global Impression) were recorded with the EIS System before undergoing antidepressant SSRI treatment. SSRI treatment follow-up was undertaken with both the EIS bioimpedance measurements (electrical conductance and dispersion $\alpha$ parameter) and by treatment responses based on the Hamilton Depression Scale (Ham-D) and CGI every 15 days over 60 days.

At day 45, two groups were established: Group 1: group with treatment response and Group 2: group with nontreatment response. At day 60, another two groups were established: Group 3: group with treatment response and Group 4: group with non-treatment response.
Comparing Group 1 and Group 2, electrical conductance measurement of the pathway between the two forehead electrodes had a specificity of 72% and a sensitivity of 85.3% (P = 0.0001), with a cutoff of 4.32. Comparing Group 3 and Group 4, electrical conductance measurements in the same pathway had a specificity of 47.6% and a sensitivity of 76.3% (P = 0.16), with a cutoff of 5.92. Comparing Group 1 and Group 2, the electrical dispersion $\alpha$ parameter of the pathway between the two disposable forehead electrodes had a specificity of 80% and a sensitivity of 85.2% (P = 0.0001) with a cutoff of 0.678. Comparing Group 3 and Group 4, the electrical dispersion $\alpha$ parameter of the same pathway had a specificity of 100%, a sensitivity of 89.5% (P = 0.0001), and a cutoff of 0.692.

Identifying attention deficit/hyperactivity disorder (ADHD) in children

Comparing ADHD group and control group children, the mean of the conductance measurements of two pathways between the forehead electrodes (from left forehead to right forehead and from right forehead to left forehead) in the ADHD group was 33.11 micro Siemens ($\mu$S) (range 2–113 $\mu$S). This was significantly higher (P = 0.001) than the mean of the conductance measurements of two pathways between the forehead electrodes of the control group (2.75 $\mu$S, range 1.75–27.4 $\mu$S). In terms of the receiver operator characteristic (ROC) results, comparing the two groups using the reference of the mean of conductance measurements of the two pathways between the forehead electrodes, the test showed a specificity of 98% and sensitivity of 80% (P = 0.0001) with a cutoff value at 7.4 $\mu$S.

Predicting the sympathetic system activity level in healthy subjects

The correlation between EIS HF spectrum analysis and HRV LF spectrum analysis variable was r = 0.76 (P < 0.001). Utilizing EIS HF spectrum analysis as the independent variable and the HRV LF as the dependent variable in a linear regression, the model was statistically significant (F[1,49] = 63.8, P = 0.001). The adjusted R2 value was 0.56. Finally, a t-test indicated that EIS HF spectrum analysis was a significant predictor of HRV LF spectrum analysis ($t = 8.0$, $P = 0.001$).

Equivalent galvanic skin response has been used in diabetes screening

The experiment showed that electrical stimulation did cause an increase in sweat response between the two electrodes. Control subjects showed a 20.2% increase in sweat rate and people with diabetes showed an 18.2% increase in sweat rate.

Discussion

The EIS has been shown to have the capacity to predict the activity level of the sympathetic nervous system. This GRS device’s capacity for this has been reported in numerous studies, and can be explained by the hypothalamus response to the temperature change according to the sympathetic system activity, via the cholinergic fiber and sweat released.

EIS conductance is a measurable marker of ADHD in children. The EIS conductance measurements between the two frontal electrodes are increased in children with ADHD, and this could be due to increased cerebral interstitial Cl$^-$ ions measured by the Cotlove coulometric chloride titrator method in the released sweat, and therefore by decrease of intracellular Cl$^-$ ions. It has been shown that the cerebral intracellular Cl$^-$ ions are correlated to cerebral oxygen/glucose. In children with ADHD, the concentration of interstitial Cl$^-$ ions is increased and cerebral oxygen/glucose is also increased, which increases ATPase pump activity and neuronal excitability, and decreases cerebral dopamine levels. EIS conductance also increases after 45 days of SSRI treatment. Research shows that the increased intracellular Cl$^-$ ions decreased cerebral oxygen/glucose and neural excitability. Therefore the decreased interstitial Cl$^-$ ions measured by the Cotlove coulometric chloride titrator method in the released sweat in the depression study are related to decreased cerebral oxygen/glucose and neural excitability, which increases GABA, which can provoke depression. The marker $\alpha$ parameter between the two frontal electrodes is more sensitive and specific than the conductance measurement in the response of SSRI treatment after 45 and 60 days of treatment.

The dispersion $\alpha$ parameter may increase in the forehead pathway during SSRI treatment, which may be due to changes in the morphology of the extracellular spaces between the two electrodes. A decrease in cerebral serotonin could be related to interstitial fluid volume and cerebral neural plasticity.
The delta of conductance in the foot pathway was the marker used in screening for prostate cancer. According to the electrochemical redox reaction at the bulk of the anode (production OH−) and cathode (production H+) electrodes, the markers could be related to acid production in the foot pathway.26 As well as this, the galvanic skin response technique provides markers to screen for diabetes.21 Research has shown a decrease in conductance measurements between the foot electrodes in type 2 diabetes patients.27 The reported decreases in conductance measurements in the foot pathway could be related to decreases in NO,27 which means that patients with diabetes have lower rates of sweating,28 and with moderate fiber damage, the sweat response may be lost.28 The poor glycemic control seen in diabetes causes precapillary damage, which in turn leads to microvascular damage.28 Precapillary damage inhibits the normal functioning of endothelial cells and blocks the normal NO pathways that cause vasodilatation. Endothelial cell damage influences vascular tone by causing a loss of distensibility in the blood vessels, which affects the ability of the vessels to dilate.28

In summary, the electrical measurements discussed in this paper can detect five physiological indicators of disease. The results of clinical investigations may be due to a number of causes which are set out in Figure 3.

**Figure 3**

![Diagram of Electrical Measurements and Clinical Investigation Results](image)

**Figure 3**

Relationship between the electrical measurements and the **clinical** investigations results.

**Conclusion**

After 10 years of development, EIS electrical measurements are better understood due to the results of clinical investigations. EIS electrical measurements have interesting clinical applications in different medical fields such as use as markers of ADHD in children and the treatment responses of SSRIs, or estimating the activity of the sympathetic system and screening for prostate cancer. To improve the specificity and sensitivity of the screening tests in diabetes, the EIS data were analyzed with data of other technologies such as heart rate variability analysis, bioimpedance to assess the body composition, and photoelectrical plethysmography.

**Acknowledgments**

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**Disclosure**

The author reports no conflict of interest in any EIS clinical investigation. The manuscript is only an assessment and analysis between the current scientific knowledge related to bio-electrical measurement and clinical investigation results.
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