SYLLABUS

WS01: Autonomic Function Tests - From Bedside To Laboratory Investigations

Saturday, November 12, 2011 14:30-18:00 Hall 3

Marrakesh, Morocco, November 12-17, 2011

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SMN SOCIETE MAROCAINE DE NEUROLOGIE

WCN Education Program

Saturday, 12 November, 2011

14:30-18:00

AUTONOMIC FUNCTION TESTS - FROM BEDSIDE TO LABORATORY INVESTIGATIONS

Chairpersons: **Heinz Lahrmann**, *Austria*
Walter Struhal, *Austria*

14:30 **HISTORY TAKING AND SUDOMOTOR TESTING**
Heinz Lahrmann, *Austria*

15:15 **CARDIOVASCULAR TESTING INCLUDING BEDSIDE TESTS**
Walter Struhal, *Austria*

16:00 *Coffee Break*

16:30 **MOROCCAN AUTONOMIC LAB: TESTS AND RESULTS**
Halima Benjelloun, *Morocco*

16:50 **CASE PRESENTATIONS AND HANDS-ON TRAINING**
Heinz Lahrmann, *Austria*
Walter Struhal, *Austria*
Halima Benjelloun, *Morocco*

16:00-16:30 *Coffee Break*

AUTONOMIC FUNCTION TESTS

Heinz Lahrmann & Walter Struhal

Contents:

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This syllabus is based on the review article "Diagnosing Autonomic Nervous System Disorders – Existing Guidelines and Future Perspectives" [1]

1. Introduction

Disorders of the autonomic nervous system (ANS) are often a severe burden to the quality of life of our patients (e.g. orthostatic intolerance in Parkinson´s disease). However, diagnostics for ANS disorders are under represented, despite their common occurrence. ANS disorders may occur primarily (primary autonomic failure, multiple system atrophy) or in the course of other diseases (Parkinson disease, diabetes mellitus, stroke, Guillain Barré syndrom). They can be of central or peripheral origin. The anatomical and functional organisation of the ANS is quite complex including structures within the brain, spinal cord and peripheral nervous system with pathways permeating all organ systems. Many feedback loops are involved to control homeodynamics and vital functions (blood pressure (BP), heart rate (HR), ventilation, body temperature, blood gas allostasis, urogenital function). To diagnose ANS disorders it is of crucial importance to test the most compromised functions. Thus, in many diseases involving the ANS more than one diagnostic test is needed. After taking a directed and comprehensive history the appropriate tests have to be selected. A questionnaire-based survey revealed that cardiovascular and sudomotor tests are the most frequently used in European autonomic laboratories [2]. These are also integrated in many modern commercially-available EMG devices. However, results have to be interpreted with great caution, particularly when comparing them to published normative values.

Many questions regarding cardiovascular regulation can be addressed using simple bed-side tests, as for instance the Schellong-test [3]. If the results are not conclusive or more detailed information is needed a set of standardised tests, the so called Ewing-Battery [4], is available. The complexity of cardiovascular dynamics may be analysed using sophisticated methods in time and frequency domain. The baroreflex represents one of the most important regulatory mechanism for BP control. Its function can be assessed by various techniques. Testing

sudomotor function provides a good measure of cholinergic sympathetic integrity and may be used clinically for early diagnosis of small fiber neuropathy.

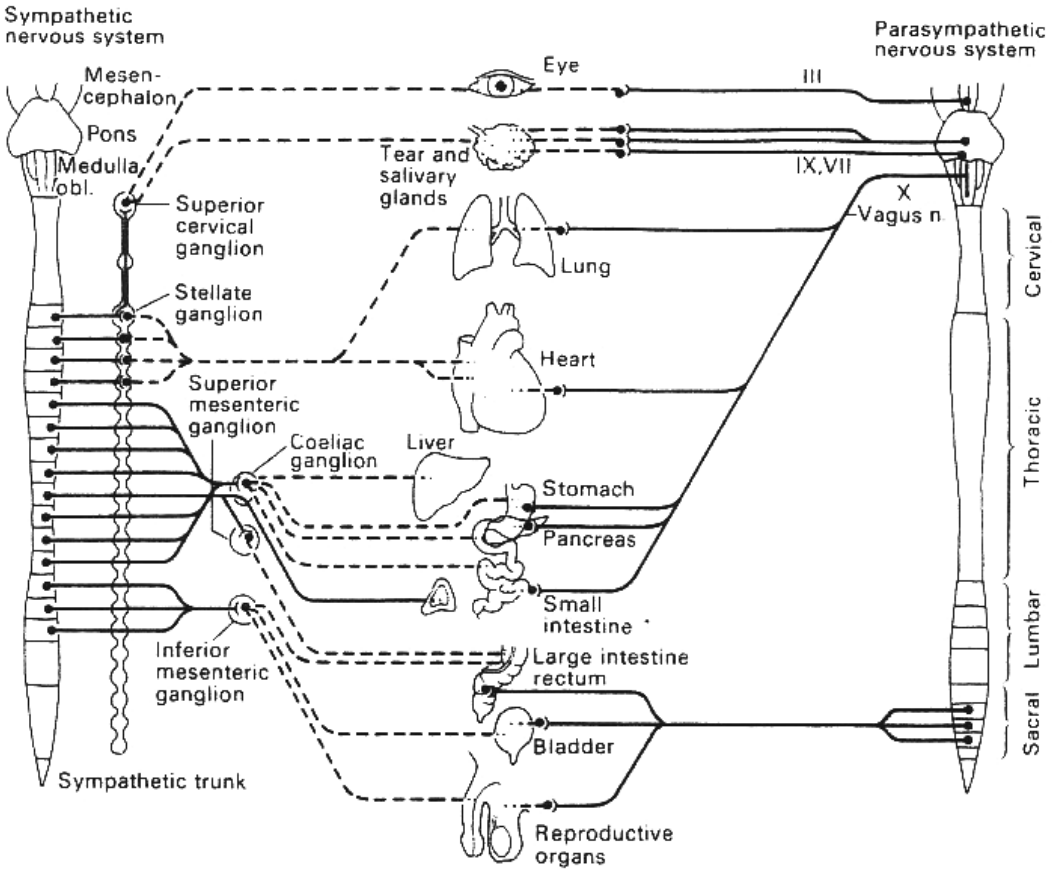


Fig. 1: Neuroanatomical organisation of the ANS

2. History taking

Diligent symptom-guided history taking is the cornerstone in the autonomic evaluation and can avoid the use of additional testing in many patients. The following aims of clinical evaluation may be definded [5]: To recognize 1. The presence and distribution of autonomic dysfunction; 2. Patterns of autonomic failure and its relation to specific syndromes; 3. Treatable disorders; 4. Further evaluation needed (e.g. autonomic laboratory); 5. Time course; 6. Effect on patient.

The most frequently encountered clinical presentation in the autonomic field concerns transient loss of consciousness (TLOC). TLOC is defined as an apparent loss of

consciousness with a rapid onset, a short duration, and a spontaneous and complete recovery [6, 7] TLOC is a differential diagnostic group comprising syncope, generalised epileptic seizures, psychogenic TLOC and a group of rare causes. A thorough step-by-step history of as many attacks as possible needs to be taken from both patients and any eyewitness. Following this approach, attending physicians can make a diagnosis based on initial evaluation (including history, physical examination and ECG) in 63% of patients with TLOC, with an overall diagnostic accuracy of 88% [8]. In most cases, a diagnosis of reflex syncope can thus be made without additional autonomic investigation. However, in case of diagnostic doubt autonomic testing may be indicated. Before ordering any kind of autonomic testing a clear hypothesis should be formulated: e.g. head-up tilt testing (HUT) is only helpful to diagnose reflex syncope or orthostatic hypotension. Rarely, HUT may also provoke psychogenic seizures, but other causes of TLOC like cardiac syncope and epileptic seizures will not be provoked by HUT. Thus, in the evaluation of a patient with syncope while jogging HUT is severely contraindicated: the circumstances of TLOC favour a cardiac cause and ordering autonomic test may cause a substantial diagnostic delay. In addition, it should be noted that additional investigations may also confuse. For example, ordering HUT or Ewing Battery in elderly patients will have a high likelihood of detecting orthostatic hypotension (OH), since OH affects up to 30% of all elderly people [6, 8]. However, the majority of cases are asymptomatic. Therefore it is crucial to obtain more evidence before assuming causality. In patients with TLOC and OH it is necessary to establish whether clinical events were typically provoked by prolonged standing, cessation of exercise (post-exercise hypotension) and ingestion of a meal (post-prandial hypotension) [6, 7]. Again, it is important to detail as many events as possible in order to recognise a clear pattern. Additionally, during the autonomic examination the patient should be questioned whether he experiences his or her typical symptoms.

Specific autonomic history [5]

Ortostatic Lightheadedness/Dizziness

Vasomotor Symptoms: Discoloration

Coldness

Sweating: Reduced?

Excessive?

Heat intolerance

Secretomotor Symptoms: Dry mouth

Dry eyes

Hypersalivation

Gastrointestinal: Postprandial Symptoms

Diarrhoa

Constipation

Abdominal Pain, Cramping

Bladder Involvement: Incontinence

Incomplete emptying

Sexual Problems: Erectile dysfunction

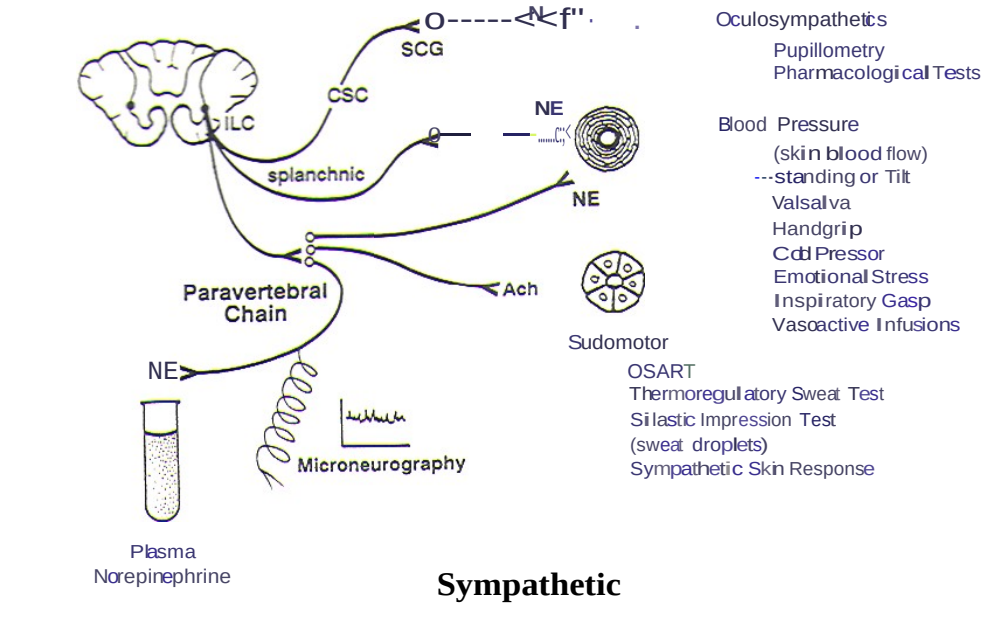
Loss of libido

Sleep Problems: Snoring

Apnea

Pupils: Glare

Blurred vision



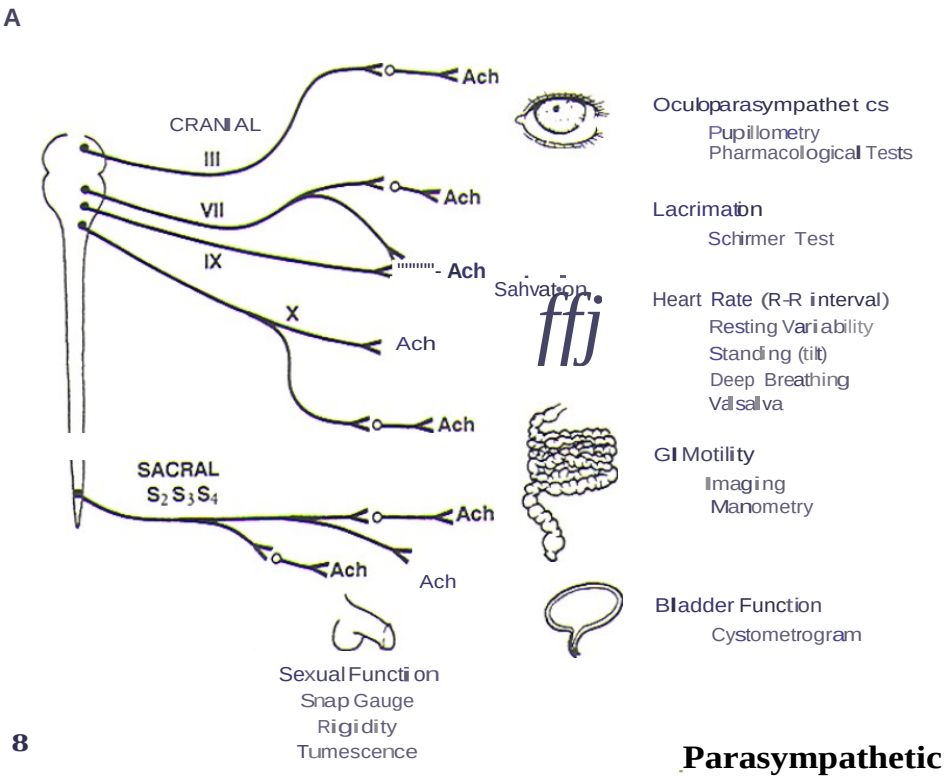


Fig. 2: Some specific tests of ANS function

3. Bedside Investigations

After a precise history, there are simple means to investigate autonomic nervous system (ANS) without a sophisticated autonomic lab, requiring only a 12-lead ECG and blood pressure measurement. Transient Loss of Conciousness (TLOC) caused by cardiac syncope has a high risk of mortality, therefore it is of utmost importance to rule out this diagnosis first. Specific hints in the history might already be a red flag to this diagnosis (structural heart disease, TLOC during supine position or while exercising, a family history of sudden death, sudden palpitations directly followed by syncope). A simple 12-lead ECG can confirm this etiology (e.g. presence of bifascicular block, inadequate sinus bradycardia, pre-excited QRS complex, QT interval abnormities, negative T waves in right precordial leads, epsilon waves and ventricular late potentials) [6]. These patients should be referred to a cardiologist immediately.

Standard somatic and neurologic examinations are needed, particularly when orthostatic hypotension is suspected. Dehydration might add to the development of orthostatic hypotension or reflex syncope. Signs of polyneuropathy of the somatic nerves might accompany autonomic neuropathy. Parkinsonian signs might hint to the diagnosis of an alpha-synucleinopathy.

Standing test

A very valuable tool for bedsite testing, especially to confirm orthostatic hypotension or Postural Tachykardia Syndrome (PoTS) is standing test. A common protocol is the Schellong test, but for sake of time, this protocol can be changed. It is much cheaper and faster than regular cardiovascular tilt table testing and is therefore recommended both in departments with access to a tilt table laboratory as pre-screening test and in departments without an autonomic lab.

Only a blood pressure meter and recording of the puls rate are needed. The patient rests in supine position for 5 to 10 minutes. Measurements are taken regularly until a steady state is reached. These data are important as the starting point for further analysis. The patient gets into upright position and another measurement is taken immediately. Blood pressure and puls rate are recorded at least every second minute for up to 10 minutes. The patient is asked to report symptoms like dizziness, fatigue, headache, nausea, etc. A decrease in blood pressure of 20 mmHg systolic and/or 10 mm/Hg diastolic within 3 minutes in upright postion proves the diagnosis of orthostatic hypotension [9]. A puls rate increase from supine to standing of more than 30 beats per minute or above 120 beats per minute within 10 minutes hints to a Postural Tachykardia Syndrome (PoTS). In few cases, standing test might provoke reflex syncope, and in these patients syncope typically occurs with prolonged standing. A study on 67 Austrian army recruits found the standing test to have a sensitivity of 61% and a specificity of 100% for PoTS (for reflex syncope a sensitivity of 31% and a specificity of 100% were noted in the same study) [3].

With these simple means, autonomic screening is available on every ward or in an outpatient department and the diagnosis might be settled without being delayed by waiting for additional tests.

Diagnosing diseases with those means:

Suspected cardiogenic syncope should be transferred to the cardiologists.

In cases with clear anamnestic hints to reflex syncope with rare events and without major injuries the diagnosis of reflex syncope might be settled. In cases with frequent syncopes, or serios injury due to syncope, as well as in cases where the history is not clearly suspicious to reflex syncope autonomic testing should be recommended

If standing test proves OH, no further autonomic testing is needed. However, etiology should be a matter of further investigations (e.g. neurogenic OH in autonomic neuropathy or Parkinsons disease or iatrogenic OH due to antihypertensive drugs). In iatrogenic OH, antihypertensive medication might be reduced. Sufficient hydration is essential. Therapeutic options are listed in the EFNS guidelines [9].

If standing test proves PoTS, no further autonomic testing is needed. Again, etiology should be further investigated [10].

4. Sudomotor Tests

Constant body temperature (homeothermia) is of essential importance for the human organism. Homeothermia is reached by autonomic, metabolic and behavioral means and mainly regulated in the hypothalamus. There is close interconnection between cardiovascular and thermoregulatory control. Heat acts as stress factor for the cardiovascular system, cooling produces bradycardia (e.g. cold face test). Thermoregulation seems to be of higher importance than cardiovascular regulation, since sweat production remains also in severe dehydrated states and might lead to heat syncope. In disorders auf the ANS, disturbances of thermoregulation are frequently seen. Investigations of thermoregulation are a valuable tool to test the integrity of the sympathetic ANS.

Disorders of sweating (hypo- or hyperhydrosis) can be focal or generalized. Evaluation of sudomotor function can provide early diagnosis of small fiber neuropathy [11], particularly in early diabetes mellitus, and is used to provide a measure of cholinergic sympathetic function. A large number of different tests are available. They can assess central and peripheral sudomotor function, as the thermoregulatory sweat test (TST) [12], or postganglionic function alone, as the quantitative axon reflex test (QSART) [13], the sympathetic skin response test (SSRT) [14], the quantitative direct and indirect axon reflex test (QDIRT) [15] and the

dynamic sweat test (DST) [16]. Patterns of sweating can be visualized by topical application of indicators such as iodinate starch or sodium alizarin sulfonate after a sufficient termal stimulus is given. Quantitative tests as QSART, QDIRT, DST, SSRT and silastic imprint test (SIT) may be used to study sweat gland activity in more detail.

SSRT. This measure of electrodermal activity provides a surrogate marker of sympathetic cholinergic sudomotor activity. An arousal stimulus (electric, acustic, deep breath) induces a change in skin potential, which is recorded from the palms and soles of the feet most often. SSR´s are reported as present or absent.

Procedure [17]:

Stimulation: median nerve on the wrist with <30mA and impulse duration of 0.1-1.2ms. Recording: 4 channel, skin electrodes palmar/plantar and dorsal of all 4 extremities, time resolution of 10s with 1s/div.

Interpretation:

- Absent SSR in all or in one channel
- 50% amplitude reduction
- Latencies

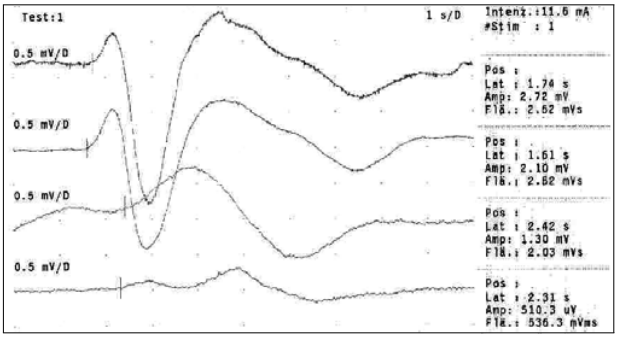


Fig. 3. Example for a 4 channel SSRT (1: r. arm, 2: l. arm, 3: r. foot, 4: l. foot) with pathologic amplitude of the left foot.

For amplitude and latency normative values have been published [17]. Although this test is very easy to perform and integrated in many comercial EMG devices there are serious

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limitations: 1. habituation, 2. high intra- and interindividual variability, 3. SSR declines with age.

TST. The test is performed in a temperature and humidity controlled chamber (45-50°C). The whole body is covered with an indicator dye and the change in color due to sweat production is documented. Asymetric patterns due to focal anhydrosis or stocking and glove distributions in length dependent neuropathy may be observed. Limitations are the visual analysis and the lack of differentiation between pre- and postganglionic lesions. The test is time-consuming and needs special equipment. To simplify means, the patient might also be covered into linen tissues without using a dye. After the sweat test is finished, the sheets are carefully removed and one might observe or photo-document the wet areas of sweating on the tissue.

QSART. This test measures postganglionic axon-reflex mediated sweat production in a small restricted area of the skin over time. The neural pathway consists of the postgangionic sympathetic sudomotor axon. To stimulate the reflex, acetylcholine is applied on the skin and follows an electric potential into the skin (iontophoresis). The axon terminal M3 muscarinic receptors are activated by acetylcholine intradermally and trigger an action potential. The action potential travels antidromically, reaches a branch point and travels orthodromically to realease acetylcholine from the nerve terminal.

Four capsules are available, testing might be performed at any skin area, where the capsules might be pressed on. However, for 4 recording sites, standard values exist: the medial forearm, the proximal leg, distal leg and proximal foot. In clinical practise only one side of the subject is studied. A multicompartmental sweat capsule is used to stimulate sweat glands by iontophoresis of acetylcholine and record sweat production.

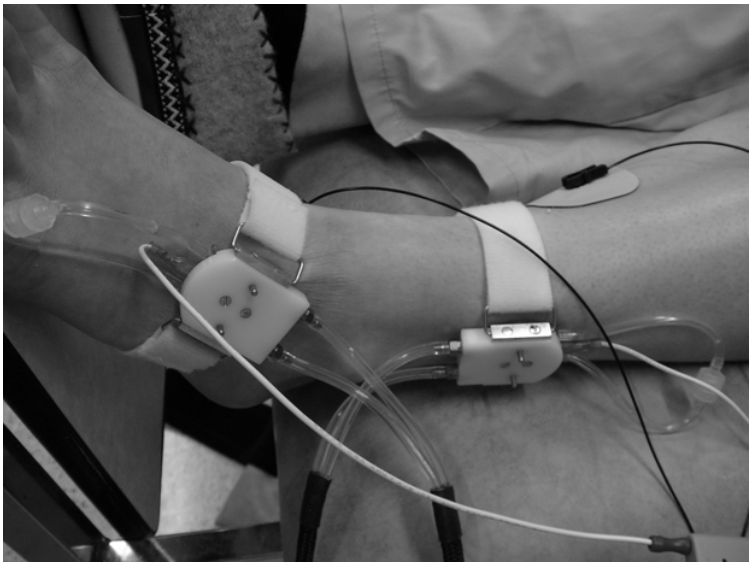

Fig. 4. Two mulicompartmental sweat capsules fixed to the distal leg and foot; electrodes are fixed next to the capsules for iontophoresis.

Evaluation: the patient should lie supine for 10 minutes. First, resting sweat production is recorded until a steady state is reached (but for at least one minute). Acetylcholine is then applied with iontoforesis by a 2mA stimulus for 5 minutes. After iontophoresis, at least 5 additional minutes are recorded to search for pathologic patterns. Measurements are defined as volume measurements over 10 minutes (by integrating 10 minutes of data collection). Several abnormal patterns of sweat responses have been identified: 1) reduced, 2) absent, 3) excessive, 4) persistent sweating or “hung up” response. The latency of sweat response is not employed as sudomotor function, since it is thought to be more of a measure of ion transfer rate and may fluctuate depending on the level of skin resistance.

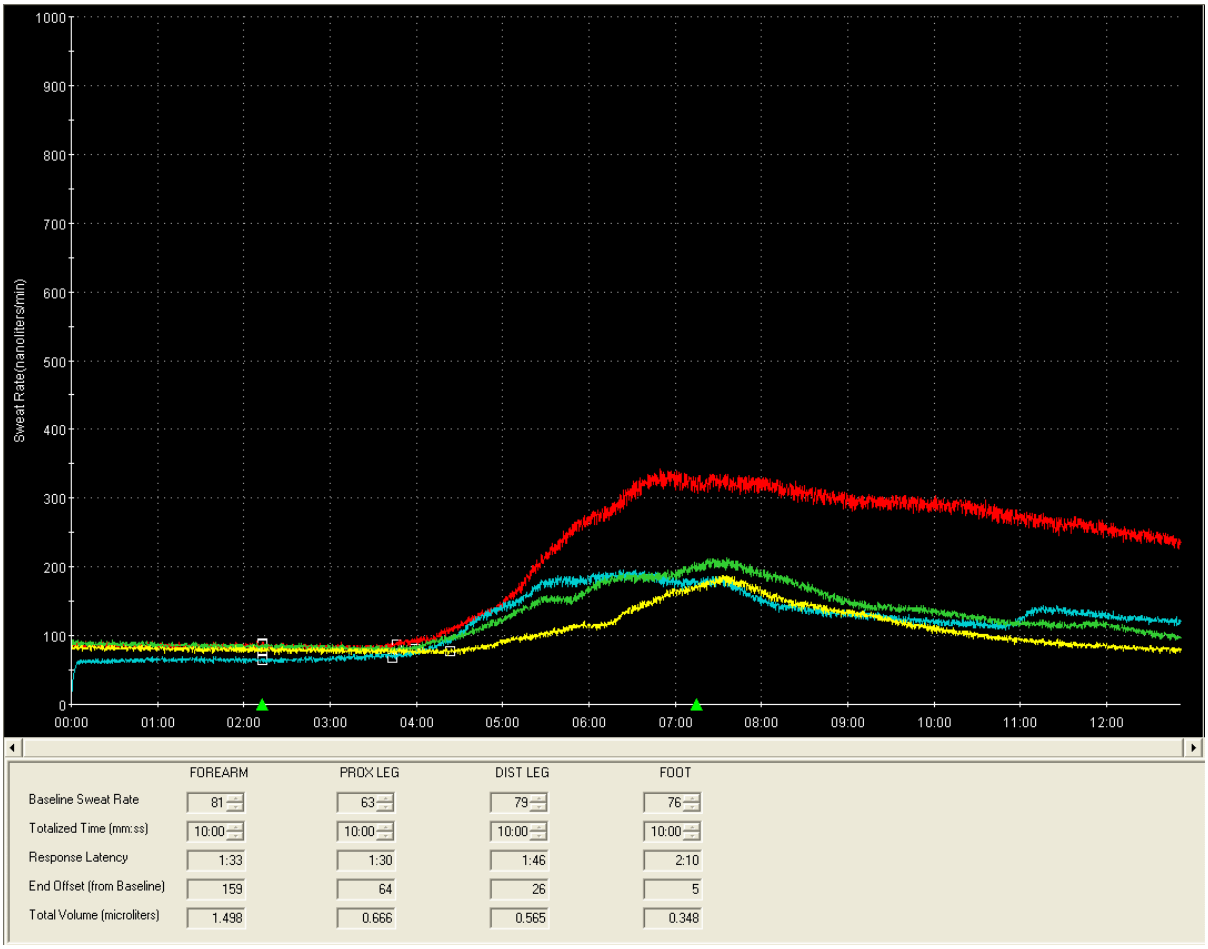

Fig. 5. Male, 31y, healthy subject: resting sweat production in nanoliter/min. A steady state is reached. After starting iontophoresis (first marker) sweat production increases and after stopping iontophoresis (second marker) decreases again.

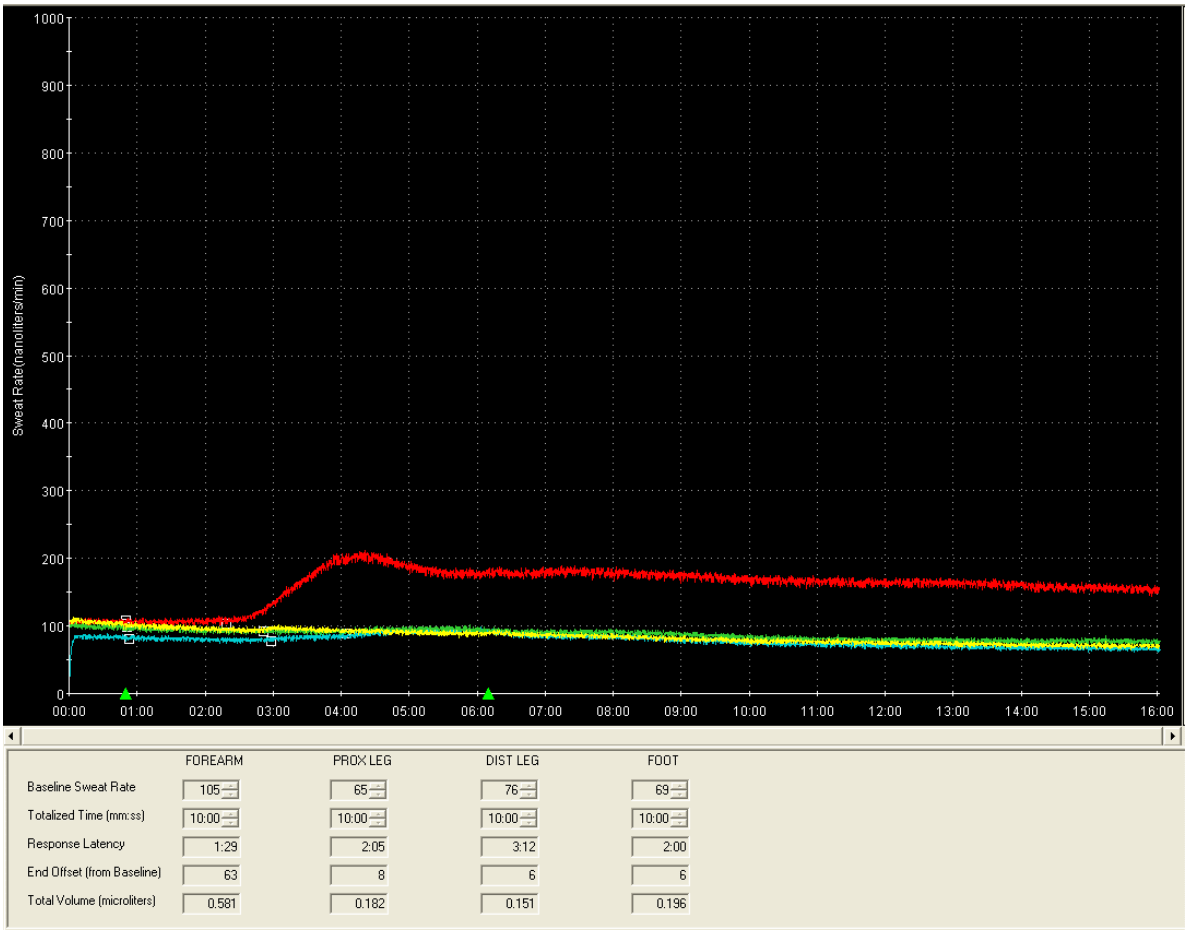

Fig. 6. Male, 82y, diabetic PNP, small fibre involvement: “hung up” response upper extremity, no response 3 capsules lower extremity.

Sweat can be sampled over a time period and analysed in correlation to other stimuli. Limitations are the expensive equipment, the very small detection area and the inability to detect preganglionic lesions. The device also allows to record resting sweat production without applying acetylcholine.

SIT. The test evaluates postganglionic sympathetic cholinergic sudomotor function by measuring the direct and axon-reflex mediated sweat response. Sweat glands are stimulated by iontophoresis of acetylcholine, pilocarpine or methacholine, followed by application of a thin layer of moldable material on the skin. Sweat droplets displace the silicone material during polymerization resulting in permanent impressions that can be quantified by various methods. Number of droplets, size and distribution are reported. Although this is probably the

easiest method to quantify sudomotor function there are several limitations: 1. the dependence of the results on the material used (polimerisation time, added surfactants, etc.), and 2. the susceptibility to artefacts, as hairs, dirt, air bubbles, skin surface texture. This method has a good spatial resolution, but renders no temporal information.

QDIRT and DST. These methods quantify sudomotor function with spatial and temporal resolution. They combine the stimulation of sweat glands and sudomotor axons by iontophoresis of a cholinergic agonist into the skin with the color change of an indicator as sweat pours out. Each sweat droplet results in a color spot which increase in perimeter and number over time. The evolving pattern of spots is recorded by high resolution digital photography or video and evaluated with automated image analysis software. Limitations are the sensitivity of the results to ambient temperature and humidity, to patient´s hydration status and caffein intake. The problem of sweat evaporation might be resolved by DST by adopting a cornstarch-powdered waterproof transparent tape. As both methods have been described only quite recently they need further investigation too prove their reproducibility and sensitivity and to establish normative data.

5. Standard Tests of the Cardiovascular System

The cardiovascular and the respiratory systems play a key role for the maintenance of homeodynamics. There exist close similarities in the central organization of both. Reflex regulation of the cardiovascular system involves the activation of different types of receptors located mainly within the heart and vessels. The information is integrated in brain stem areas and, through negative feedback mechanisms, an appropriate response is generated. The peripheral autonomic nervous system conveys this response to the target organs.

Autonomic testing has a clear emphasis on the cardiovascular system and its interactions with the respiratory system due to the easiness of non-invasive recording of cardiovascular variables. Based on this premise a standard battery of autonomic challenge maneuvers was suggested by Ewing and Clarke [4]. For clinical evaluation Valsalva maneuver, active standing and deep breathing are the most valuable tests; these manoeuvres will be detailed in this section. There are many other tests activating sympathetic or parasympathetic responses include the cold pressor test, the cold face test, the sustained hand grip test, squatting, coughing, and mental arithmetic [18]. It should be stressed that no single test can provide a global assessment of autonomic function. The normative values of these tests depend upon a large number of factors, including the specific laboratory conditions (e.g. room temperature, instrumentation), the protocol followed (e.g. duration of the stimulus, body position during and prior to testing) as well as patient-related factors (e.g. age, medication, use of caffeinated drinks etc.). Thus, caution has to be taken when interpreting individual results on the basis of published normative values. From a clinical point of view it should be stressed that autonomic challenge maneuver tests are directed towards the determination of autonomic failure, as may be seen in the context of orthostatic intolerance. However, the Ewing battery is usually not of help to detect autonomic overactivity as seen in reflex syncope. For these patients head-up tilt testing may be indicated.

Valsalva maneuver. The Valsalva maneuver assesses the sympathetic as well as the parasympathetic reaction to baroreflex activation. The test subject is asked to exhale into an almost occluded mouthpiece and to maintain an expiratory pressure of 40 mmHg for 15 s. A very small hole in the mouthpiece keeps the glottis open. The test is devided into four phases. Phase 1 occurs during the first 2–3 s of the forced expiration and shows a brief decrease in HR and increase in BP due to mechanical compression of the aorta. During phase 2 BP first decreases and then increases in the late portion of this phase. Phase 3 describes the first 1–2 s

after release of the expiratory strain with a consecutive decline in BP and increase in HR. Finally, phase 4 shows a BP overshoot due to the persistent sympathetic activity together with a normalization of venous return. This BP increase mediates a baroreflex-induced bradycardia and is quantified with the Valsalva ratio: the ratio of the highest HR during expiration and the lowest HR during the first 20 s after the release of strain. Results depend on the position, age and gender of the tested subject as well as the duration and intensity of the expiratory pressure. In patients with autonomic dysfunction, there typically is a loss of both: the BP overshoot and the reflex bradycardia.

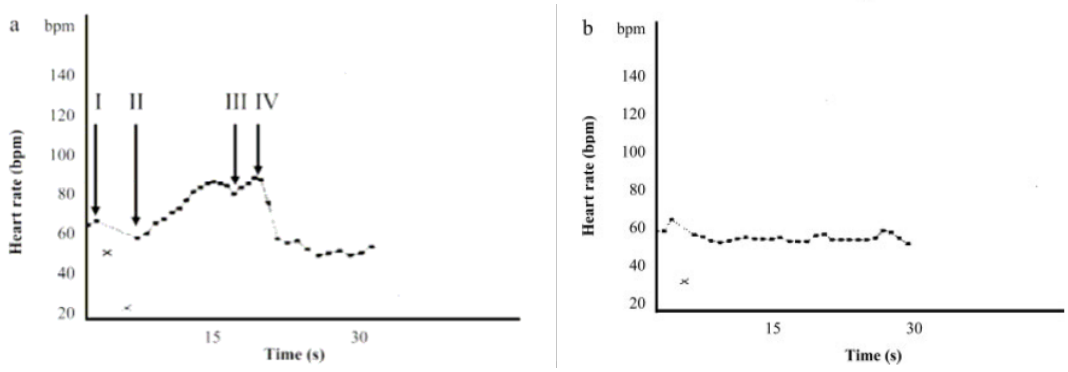

Fig. 7: Normal heart-rate variability during a Valsalva maneuver in a 36-year-old subject, showing four defined phases (I–IV) and baroreflex-mediated bradycardia **(a)**. Absent modulation of heart rate in a 37-year-old diabetic patient. During strain, there is no increase of heart rate; after release of the strain, there is no reflex bradycardia **(b)**. (bpm, beats per minute; s, seconds.). From [19]

Deep (metronomic) breathing. Respiratory sinus arrhythmia with inspiratory acceleration and expiratory slowing of HR depends on the rate of breathing and is maximal at a rate of 5-6 breaths per min. Changes of HR with deep respiration can be considered a parameter of parasympathetic cardiac control. Usually, HR variability is assessed with the patient breathing metronomically at a rate of 6 cycles per min for 3 minutes. The minimum and maximum HR of the averaged five largest consecutive responses are determined and the difference between maximum and minimum HR and the expiratory/inspiratory ratio are calculated. HR variability during deep breathing is influenced by the position of the test subject, the rate and depth of breathing, hypocapnia, sympathetic activity, salicylates and other drugs, as well as body

weight. A decreased HR variability is an important indicator of cardiac vagal denervation but it should be noted that normative values decrease with age and with increasing resting HR.

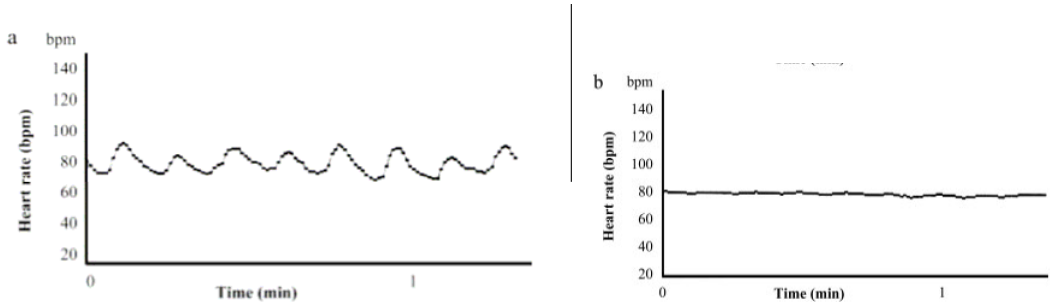

Fig. 8. Heart-rate variability (HRV) during 6/min breathing: normal HRV in a 39-year-old control **(a)**; absent HRV in a 38-year-old patient with diabetic autonomic neuropathy **(b)**. (bpm,beats per minute.). From [19]

Active standing. To evaluate the initial cardiac responses to active standing up, Ewing introduced the 30/15 HR ratio. The index calculates the ratio between the shortest R-R-interval around the 15th heart beat and the longest R-R-interval around the 30th beat after standing up. Atropine abolishes the bradycardiac response indicating that the 30/15 ratio is a parameter of cardiovagal function. In patients without secondary relative bradycardia, responses can be quantified by calculating the difference between the baseline HR and the highest HR occurring within 15 s after standing up. Normal values for both methods are age-dependent. According to the Consensus Committee of the American Autonomic Society and the American Academy of Neurology [20], a fall in systolic pressure of at least 20 mmHg or in diastolic pressure of at least 10 mmHg within 3 min of standing or head-up tilt is considered to define orthostatic hypotension [9].

Head up tilt test (HUT). The head-up tilt test complements the autonomic evaluation of active standing as it, conceptually, allows analysing the hemodynamic modifications elicited by baroreceptor reflex activation without the interference of the muscular pump of the legs. Further it should be performed in patients who cannot stand up actively and orthostatic dysregulation is highly suspected [9]. In normal subjects a decrease in blood pressure related to a re-distribution of blood due to gravity is observed which, in turn elicits an activation of

baroreceptors [21]. Due to feedback mechanisms, an activation of the sympathetic nervous system together with a decrease of parasympathetic activity occurs to re-establish blood pressure levels. Classically, the haemodynamic changes to HUT show two phases: an earlier cardiovascular acute response with a duration of 30s and a second phase – the stabilization period – composed of two periods: an earlier adaptation period occurring 1-2 min after orthostasis and a second late response to prolonged orthostasis lasting for more than 5 minutes [19, 21].

To perform this maneuver, after a resting period of 5 minutes, subjects are head-up tilted to 60 to 70º on an electrical table at a constant speed and kept upright for a period of 5-10 minutes. After this period, they are returned to supine position. The changes in blood pressure and heart rate are evaluated against normative data [18]. In patients with reflex syncope, HUT of 5-10 minutes is usually not sufficient to provoke syncope. In contrast to the autonomic challenge maneuvres, HUT can not only determine autonomic under-reactivity, as seen in e.g. orthostatic hypotension, but is also able to provoke reflex syncope. For the latter indication the subject is tilted for up for 40 min. In elderly with a clinical history of carotid sinus hypersensitivity, HUT may be combined with sinus carotis massage.

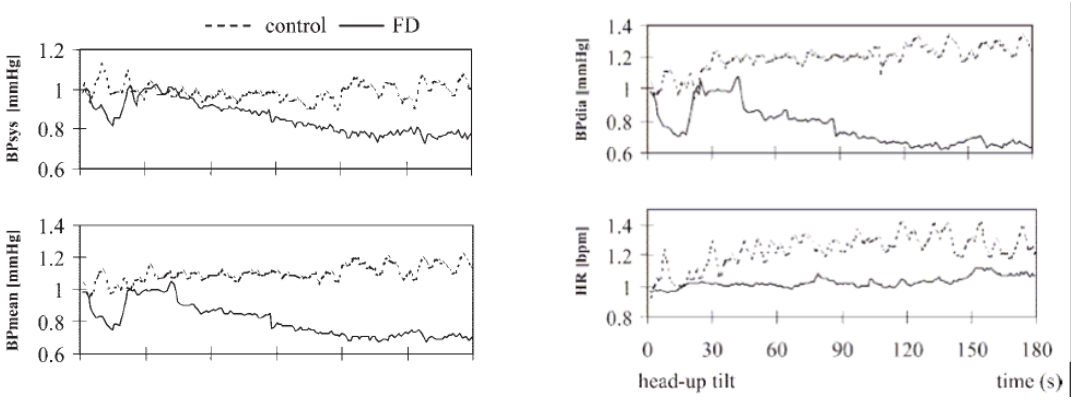

Fig. 9. Blood pressure (BP) and heart rate (HR) during head-up tilt in a control and in a patient with familial dysautonomia (FD). (BPdia, diastolic blood pressure; BPmean, mean blood pressure; BPsys, systolic blood pressure.) The patient shows orthostatic hypotension and absent reflex tachycardia. From [19].

6. Analysis of cardiovascular signal variability

HR and BP variability can also be analysed in frequency domain using Fast Fourier Transform (FFT), Wavelet Transform (WT) or Huang-Hilbert Transform (HHT) (see below) to evaluate the dynamics of sympathetic and parasympathetic innervation of the cardiovascular system. Patients with autonomic failure, for example orthostatic hypotension, show different pathological profiles of response: delays in these adaptive responses, dysynergy between blood pressure and heart rate responses and/or exaggerated responses like orthostatic hypotension, postural orthostatic tachycardia or syncope.

Cardiovascular variables show rhythmic oscillations and stochastic fluctuations along time as result of the summation of the cardiovascular regulatory processes. Biological signal analysis techniques have been applied to these signals to detect pathologic patterns that can help to improve diagnoses and follow-up in autonomic disorders. In particular, the application of FFT and autoregressive spectral analysis to heart rate and blood pressure signals has made a very important contribution to autonomic evaluation. FFT, by using sinus functions of different frequencies and amplitudes, decomposes the signals allowing a definition of a power spectrum where two major ranges of frequencies for human subjects can be recognized: low frequencies (LF [0.04-0.15 Hz]) and high frequencies (HF [0.15-0.4Hz]) [22]. For oscillations in heart rate or RR intervals, LF has been related mainly to sympathetic outflow although there may be also some parasympathetic influence due to slow breaths, while HF is related to parasympathetic outflow and respiratory rhythm. The ratio LF/HF has been widely used as an indicator of the autonomic balance [23]. However, FFT analysis shows important limitations as it requires a stationary signal, a long period of data collection. It is not useful to locate and follow changes of a frequency over time. Wavelet analysis has been used to overcome these limitations and perform a time-frequency analysis which allows for the correlation of LF and HF changes with any particular external signal or event [21, 24].

Recently, a modified HHT has been proposed as a more suitable tool for clinical autonomic evaluation as it renders a higher time-frequency resolution and represents nonlinear processes better [25]. These new methods have to be evaluated for their validity and usefulness for ANS testing in the future.

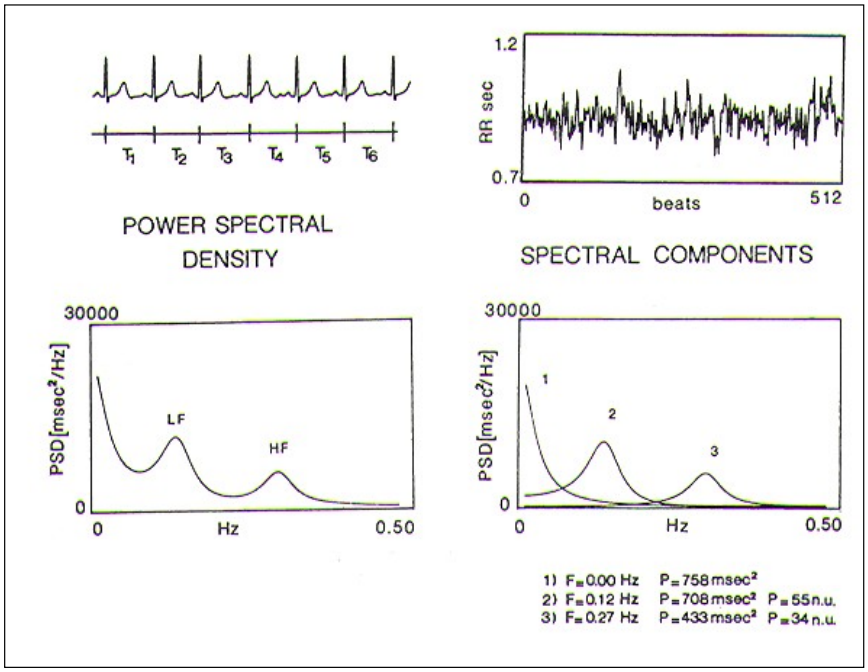

Fig. 10. ECG, HF, power spectral density and its components. From [23].

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