Cardiovascular and neurohumoral responses to i.v. l-arginine in multiple system atrophy (MSA) and pure autonomic failure (PAF)

J. Kimber, S. Puvi-Rajasingham L. Watson, C.J. Mathias
Neurovascular Medicine Unit, Division of Neuroscience and Psychological Medicine, Imperial College School of Medicine at St. Mary's Hospital, London, UK
Autonomic Unit, University Department of Clinical Neurology, National Hospital for Neurology and Neurosurgery Queen Square & Institute of Neurology, University College London, UK

Basal release of nitric oxide (NO) from the vascular endothelium of resistance vessels maintains a vasodilatory tone, opposed by sympathetically mediated vasconstriction that regulates blood pressure (BP) [1]. Systemic infusions of the NO-precursor l-arginine lowers BP in normotensive [2] and hypertensive man [3] although this is not so in other studies [4]; these differences may be due to the effects of l-arginine on a number of hormones. In neurally mediated syncope, orthostatic hypotension (OH) is associated with increased urinary cGMP levels, suggesting increased NO synthesis. [5] The contibution of the endothelial-NO vasodilator system to abnormal BP control and OH in primary chronic autonomic failure syndromes (AF), is not known. We therefore studied the effects of i.v infusion of l-arginine in 20 patients with AF; 10 MSA (mean age 65 m/f 7:3) and 10 PAF (mean age 59 m/f7:3). None had been taking antiparkinsonian or pressor medication for >1 week prior to the study, except low dose fludrocortisone, which was stopped for 24 hrs. All studies were carried out in a temperature controlled laboratory following an overnight fast. After 30 mins supine rest and antecubital vein cannulation, l-arginine (0.5 g/kg in 250 ml 0.9% saline) was infused over 30 mins. Blood pressure and heart rate (HR) using an automated sphygmomanometer was recorded every 5 mins. Venous blood was collected for measurement of plasma noradrenaline (NA) and adrenaline (A) at 15 min intervals for 90 mins. Basal levels of mean arterial pressure (MAP) were similar in MSA and PAF. Resting HR was higher MSA (74 ± 4 beats/min) than in PAF (61 ± 2), $p < 0.05$. Following l-arginine, MAP fell similarly in both groups; MSA (131 ± 6 to 98 ± 9 mmHg) and PAF (130 ± 10 to 101 ± 8), nadir 30 mins with a recovery after 60 mins. In both groups HR was unchanged. Basal levels of plasma NA and A were lower in PAF (125 ± 25 pg/ml and 5 ± 3) than MSA (229 ± 29 and 22 ± 8), $p < 0.05$. After l-arginine, no change in plasma NA was detected in PAF, unlike MSA in whom there was a rise at 45 mins (369 ± 55 pg/ml, $p < 0.05$). Plasma A was unchanged in both groups. In conclusion, l-arginine lowered BP in both MSA and PAF; this was to a greater extent and more prolonged than reported in normal man. There was no accompanying rise in HR in either group. In MSA, unlike PAF, there was a late rise in plasma NA but not A. The results suggest excessive vasodilatation to NO in primary AF subjects, although a vasodilatory effect, through other released substances, like insulin, cannot be excluded.

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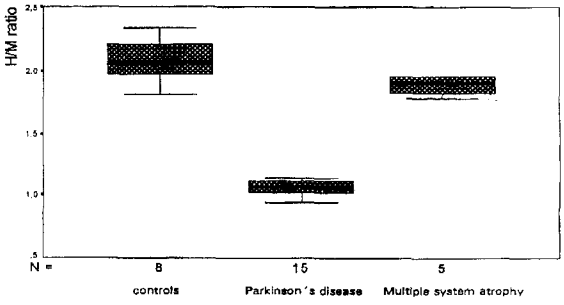
Differentiation between idiopathic Parkinson's disease with autonomic failure and multiple system atrophy by meta-[^{123}I]Iodobenzyl-guanidine scintigraphy of cardiac sympathetic efferents

S. Braune, M. Reinhardt, R. Schnitzer, C.H. Lücking
Dept. of Neurology, University of Freiburg, Germany

Scintigraphy with meta-[^{123}I]Iodobenzyl-guanidine (MIBG) allows the assessment of localisation and functional integrity of postganglionic cardiac adrenergic neurons. The ratio of MIBG uptake of the heart and mediastinum serves as an index of cardiac innervation.

We investigated eight control subjects between 21 and 70 years, 15 patients with Parkinson's disease and autonomic failure and 5 patients with MSA. The healthy subjects showed a mean ratio of 2.02 (SD 0.17, range 1.85 to 2.4) independent of age. The mean heart/mediastinum ratio in patients with Parkinson's disease was 1.06 (SD 0.06, range 0.97 to 1.13) suggesting a relevant postganglionic pattern of autonomic nervous system involvement. As autonomic failure in multiple system atrophy (MSA) is caused by degeneration of central and preganglionic autonomic neurons, MIBG scintigraphy should distinguish between the two conditions. MIBG scintigraphy in all MSA patients was normal (mean heart/mediastinum ratio of 2.03, SD 0.39). These findings were independent of the severity of autonomic failure and duration of disease in both patient groups.

MIBG scintigraphy of cardiac neurons appeared to allow the discrimination between Parkinson's disease with autonomic failure and MSA not only in comparison between groups of patients but also in single patients, even at an early stage of the development of autonomic failure.



Dysautonomia secondary to apomorphine challenge test for diagnosis of Parkinson's disease

I. Reuter, J. Flowers, C. Agapito, J. Mills, C. Clough, K. Ray Chaudhuri
Movement Disorders and Autonomic Regional Unit, King's Neurosciences Centre, King's College Hospital

Apomorphine, a D1 and D2 selective dopamine agonist, is an established therapy for advanced Parkinson's disease patients with fluctuating motor responses and long term levodopa syndrome. Apomorphine, owing to its very short duration of action, has also been used as a challenge test for the diagnosis of Parkinson's disease and also to assess dopaminergic responsiveness in akinetic rigid syndromes. In this study we have assessed the dopaminergic response and diagnostic accuracy, and also autonomic side effects, of apomorphine challenge test performed in 50 parkinsonian patients (mean age 57 ± 12.8 years, duration of levodopa treatment 12.2 ± 6 years and mean levodopa dose/day (700 ± 300mg) on an outpatient basis. Anecdotal reports have linked apomorphine challenges with a first pass effect and also syncopal episodes; autonomic side effects were specifically assessed. Of the 50 patients studied, 40 were already on chronic apomorphine infusion and

injection treatment and 10 patients were drug naïve in whom apomorphine was used for diagnostic purposes.

Patients were given domperidone, a peripherally active dopamine antagonist, 20mg three times a day for 3 days to prevent apomorphine-induced nausea and vomiting, and were studied after an overnight fast and pre-apomorphine ECG to rule out any significant cardiac ischaemia, heart block or tachy/brady arrythmias. Subcutaneous apomorphine was injected in a standard fashion, starting at a dose of 1.5mg and increasing to 10mg with 1.5mg increments at 40 minute intervals. Pre and post apomorphine challenge motor assessment included alternative unilateral hand tapping for 30 seconds, timed walking test and the motor United Parkinson's Disease Rating Scale. A brief autonomic battery was carried out before and after apomorphine challenge test and consisted of supine and erect heart rate blood pressure responses, isometric exercise and hyperventilation in selected cases and 30/15 ratio. A positive apomorphine response was defined by a decrease of more than 20% of the UPDRS motor score.

Forty five out of 50 patients had a positive response to apomorphine; this included 8 out of the 10 drug naïve parkinsonian patients. A negative apomorphine challenge test correctly predicted a Parkinson plus syndrome (3 patients with progressive supranuclear palsy and 1 with a cerebellar variant of MSA). The time to switch on from the "off" stage was 15.5 ± 12 min while the mean duration of "on" period after apomorphine challenge was 65 ± 29 min. A significant postural hypotension with a mean drop in systolic blood pressure of 32 ± 8 mmHG was seen in 6 patients, most noted in walking after apomorphine challenge. The ability to perform isometric exercise and hyperventilation responses however significantly improved after apomorphine challenge and are likely to have correlated with the reduction in ability to perform these manoeuvres in the "off" state being reversed after apomorphine. Of the 6 patients with significant orthostatic hypotension 1 suffered a syncope. This was associated with a compensatory rise in heart rate. In one patient, apomorphine infusion produced a transient pressor response which normalised after 3 minutes. Nausea was observed in 2 patients in spite of domperidone pre-treatment.

We conclude that apomorphine challenge is an extremely useful test for assessment of doparesponsiveness and may be used for the diagnosis of Parkinson's disease when the clinical features are not typical, and also to predict Parkinson plus syndrome. However autonomic side effects, in particular abnormalities of blood pressure responses during postural change and significant postural hypotension may complicate apomorphine challenge test in spite of using a peripheral dopamine blocker, domperidone. This postural hypotension appears to occur irrespective of a direct cardiac effect of apomorphine and may well be linked to its peripheral action and also to a partial or incomplete peripheral dopamine receptor blockade by domperidone. These factors need to be considered when performing apomorphine challenge tests and the clinical implication is that timed walking after apomorphine challenge in patients who have a resting postural hypotension prior to apomorphine challenge may not be advisable.

The relationship of uro-genital dysfunction to other features of autonomic failure in MSA

K. Kirchhof, C.J. Mathias, C.J. Fowler

The inclusion of bladder and sexual dysfunction as symptoms of "autonomic failure" implies that there is a common pathophysiology for these symptoms and postural hypotension. However because of a clinical impression that uro-genital symptoms could often occur without symptoms of postural hypotension, we carried out a retrospective study of 98 patients with a diagnosis of probable MSA. They had been referred to Department of Uro-Neurology between 1992-6 either for investigations or for advice on management of urinary dysfunction. There were 27 female and 71 male, with a mean age of onset of symptoms at 50 and 52 years respectively.

Results: Urinary symptoms were present in 98%; 40% had no other symptoms of autonomic dysfunction, postural hypotension in particular. There were no patients who had symptoms of postural hypotension without also having uro-genital symptoms.

Inquiries of sexual function in 63 of men revealed male erectile dysfunction (MED) was a complaint in all. At the time of assessment i.e. when a diagnosis of "probable" MSA was being made, 32% with MED had no other symptoms of autonomic failure but 95% had urinary symptoms. In 58% MED had preceded the onset of bladder symptoms.

Sphincter EMG was abnormal (mean duration of 10 motor units>10.0 ms) in 91% while standard cardiovascular autonomic function tests were considered abnormal in 68%. In the men with MED, sphincter EMG was abnormal in 91% and autonomic function tests were abnormal in 78%.

Discussion: We conclude that in a proportion of patients with MSA there is a dissociation between the results of standard cardiovascular autonomic function testing and uro-genital abnormalities in MSA. This probably indicates variable involvement in a progressive disorder in which different systems are affected in an unpredictable manner. Detection of dysfunction in these systems is probably dependent on both sensitivity of testing and especially in the cardiovascular system, on non autonomic mechanisms that are recruited to compensate for the autonomic deficits. The involvement of both urinary and genital (in the male) systems indicates these disorders may be due to similar impairment within CNS structures in MSA.

Reflex nature of the response to primary thoracic blast injury

M. Ohnishi, E. Kirkman, *P. Watkins, *G.J. Cooper
Department of Biological Sciences, University of Durham, Durham, DH1 3LE and *DERA, Medical Countermeasures, CBD, Porton Down, Salisbury, SP4 0JQ

Primary blast injury to the thorax induces a short-latency bradycardia, hypotension and apnoea, followed by the development of pulmonary oedema (Krohn *et al.,* 1942). We are interested in the mechanisms underlying this response. A candidate reflex which may mediate the response to blast is that elicited by activation of pulmonary afferent C-fibres, since this reflex produces a similar triad of bradycardia, hypotension and apnoea (Daly & Kirkman, 1988). The pulmonary afferent C-fibres are carried in the vagus and induce a bradycardia by increasing vagal efferent activity. The aim of the current study was twofold: to determine whether the response to thoracic blast is a reflex with a vagal afferent pathway and hence can be blocked by vagotomy, and to assess whether the bradycardia is due to an increase in vagal efferent activity, and hence can be blocked by atropine. Aspects of this work have already been published (Ohnishi *et al.,* 1998a, b).

Experiments were performed on 4 groups of 8 male Wistar rats (240–263g) anaesthetised with alphadolone/alphaxalone (17–21 $mg.kg^{-1}.h^{-1}$ i.v.). Body temperature was maintained constant at 38.0 ± 0.1°C (mean ± s.e. mean) using external heating. In Groups I and IV the cervical vagi were exposed bilaterally but not sectioned (sham vagotomy), whereas they were sectioned in Groups II and III (vagotomy). 10–15 min after vagotomy or sham vagotomy baseline cardiorespiratory measurements were made and the animals subjected to a blast wave focused on the ventral thorax (Groups I and II), or the sound of blast (Groups III and IV, sham blast). Following blast in animals with intact vagi (Group I) there was a significant ($P < 0.05$, paired t-test) fall in heart rate (HR) from 459 ± 9 to 128 ± 11 $beats.min^{-1}$ (latency of onset 4.3 ±

0.3 s), significant reduction in mean arterial blood pressure (MBP) from 128 ± 4 to 35 ± 4 mmHg (latency of onset 2.0 ± 0.1 s) and apnoea lasting 28.3 ± 2.3 s. In vagotomized animals (Group II) there was only a small fall in HR from 469 ± 7 to 414 ± 13 beats.min^{-1}, the apnoea was absent, and the hypotension attenuated (MBP fell from 124 ± 3 to 70 ± 6 mmHg in this group). Sham blast (Groups III and IV) had no significant cardiovascular or respiratory effects. The effects of atropine on the response to blast was assessed in a further two groups of animals with intact vagi: Group V (n = 9) given 0.9% saline (1 ml.kg^{-1} i.v.) and group VI (n = 8) given atropine sulphate (0.3 mg.kg^{-1} i.v.) 10–15 min before exposure to blast. In the saline treated control animals (Group V) the response to blast was similar to that reported for Group I. Pretreatment with atropine (Group VI) attenuated significantly the bradycardic response to blast, with HR now only falling to 423 ± 8 from 475 ± 11 beats.min^{-1}. Atropine did not modify the hypotension or apnoea associated with blast.

These results indicate that thoracic blast injury produces a triad of bradycardia, hypotension and apnoea. The apnoea, most of the bradycardia and a portion of the hypotension are reflex in nature with the afferent and/or efferent pathways carried in the vagus.

This work was supported by DERA, Porton Down.

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Left ventricular mechanoreceptors are relatively unimportant in cardiovascular control

C. Wright, M.J. Drinkhill, R. Hainsworth
Institute for Cardiovascular Research, University of Leeds, UK

Left ventricular mechanoreceptors are widely believed to be of major importance in cardiovascular control and to be involved in several clinical conditions including syncope and heart disease. However, previous work has not effectively separated the stimulus to ventricular receptors from those in the coronary arteries.[1,2] We now report results of experiments in which discrete physiological stimuli were applied to either the left ventricle or to the coronary baroreceptors.

In dogs anaesthetised with chloralose, the chest was opened and a cardiopulmonary bypass connected. A cannula tied in the ascending aorta allowed control of coronary artery pressure with a balloon tied at the aortic valve separating coronary from ventricular pressures. Ventricular pressure was changed by applying various pressures to a cannula inserted into the ventricle through its apex. Pressures distending aortic and carotid baroreceptors were also controlled. Vascular resistance responses were assessed as changes in perfusion pressure (constant flow) to the systemic circulation.

In six dogs coronary, carotid and ventricular pressures were independently changed between 60 and 180 mmHg. The responses of systemic pressure were: to coronary −38.9 ± 6.1% (mean ± S.E.M.); carotid −34.4 ± 2.9%; and ventricular −12.0 ± 2.5%. The response of systemic perfusion pressure was significantly smaller for changes in left ventricular pressure than for either the carotid ($P < 0.05$, paired t test) or coronary pressure changes ($P < 0.05$). There was no significant difference between the responses to changes in coronary or carotid pressure.

These results indicate that left ventricular mechanoreceptors are unlikely to have a major role in cardiovascular control and suggest that the reason that previous investigations believed them to be of importance was because coronary baroreceptors were also being stimulated.

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Assessment of the autonomic control of the heart in patients with cardiac syndrome X

A. Cevese, R. Cemin[1], G. Gulli, P. Pancera[2], C. Vassanelli[1]
Departments of Human Physiology, [1]Cardiology, and [2]Internal Medicine, University of Verona, Italy

To test whether in cardiac syndrome X (angina, inducible myocardial ischemia and normal coronary angiography) (SX) an increase of the sympathetic drive to the heart is involved[1], we studied 15 patients (58 ± 2 years) with SX. We recorded 10 min time series of R-R period (RR) in ms and systolic blood pressure (SAP) in mmHg from a standard ECG and finger arterial pressure (Finapres), in supine position (S) and after passive 60° tilting (T). We performed spectral analysis of the time series by an autoregressive method, to quantify low (LF) and high (HF) frequency oscillations. Values are reported as mean ± standard error.

We selected 10 patients (SX+) who displayed a systematic increase of LF power of SAP (from 4.4 ± .5 to 9.4 ± 1.6 mmHg^2) and lack of any change in RR time and frequency domain values in T, with relative tachycardia (RR = 768 ± 29 ms) and reduced HF power of RR (62 ± 21 ms^2) in S. The remaining 5 patients (SX-) displayed lower heart rate (RR = 932 ± 50 ms) and higher HF power of RR (215 ± 126 ms^2) in S, and the expected changes of RR in T. On the basis of previous experience[2], we suspected that in SX+ the parasympathetic control of the heart was impaired. Thus, we performed a set of standard vagal stimulation tests (supine/standing/supine, squatting, deep breathing, 40 mmHg Valsalva manoeuvre and cold face) on 5 SX+ and 2 SX-. The pooled score of the tests indicated vagal impairment in 4 SX+. The remaining SX+ was asymptomatic when tested for vagal function.

We suggest that in about 2/3 of SX patients a specific autonomic dysfunction exists, consisting in a reduced resting vagal tone, not a sympathetic hypertone, as suggested by others[1]. This conclusion may be important both for the assessment of causal factors in at least a part of SX patients and for therapeutic interventions.

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Comparison of haemodynamic changes during orthostatic stress in healthy individuals and in patients with poor orthostatic tolerance

C.M. Brown, V. Wight, R. Hainsworth
Institute for Cardiovascular Research, University of Leeds, Leeds, UK

During orthostatic stress, pooling of blood in the veins and increased capillary filtration in the dependent regions contribute to a decrease in the venous return and cardiac output. If these changes are not adequately compensated for by reflex vasoconstriction then syncope may occur. In this study, we compared the haemodynamic responses to orthostatic stress in twelve healthy volunteers and twelve patients with unexplained syncope.

The volunteers and controls underwent an orthostatic stress test, consisting of head-up tilting followed by the addition of graded lower body suction. Recordings were made of heart rate (ECG),

blood pressure (Finapres), brachial blood velocity (Doppler) and leg volume changes (impedance plethysmography). Orthostatic tolerance (time to presyncope) was significantly greater in the controls (32.2 ± 2.9 min) than in the patients (20.7 ± 1.8 min) ($P = 0.025$). Head up tilt resulted in immediate changes in regional volumes, assumed to be due to venous pooling, followed by slower continuous increases (assumed to be capillary fluid transudation). The initial leg volume changes were not significantly different in the two groups, however the patients had a higher secondary rate of volume change than the control subjects (4.67 ± 0.37 versus 3.41 ± 0.39 ml/min, $P = 0.028$). The increase in forearm vascular resistance (measured as mean arterial pressure divided by brachial blood velocity) in the control subjects was significantly greater at all stages of the test than in the patients (max. changes: controls 89.4 ± 11.27%, patients 54.6 ± 8.95%, $P < 0.05$).

These results indicate that poor orthostatic tolerance is related to excessive capillary fluid loss during orthostatic stress, poor vasoconstrictor responses, or both.

These experiments were approved by the United Leeds Teaching Hospitals Ethical Committee and were funded by the British Heart Foundation.

Paleoneurobiology

Pam Milner[1], Abi Belai[1], Charles V. Hoyle[1], Martin Appenzeller[2], Otto Appenzeller[2]

[1]Autonomic Neuroscience Inst. and Dept. of Anatomy & Developmental Biology, University College London UK
[2]NMHEMC Research Foundation, Albuquerque, NM USA

Background: We use the term *paleoneurobiology* for the study of the neurobiology of ancient humans and animals. We have published the immunohistochemical finding of neurochemicals in ancient embalmed Egyptian sural nerves[1]. We now report additional studies on ancient human remains.

Methods: All tissues were rehydrated prior to processing. One naturally mummified ileum from the Atacama desert[a] 1300 years old and 3 naturally mummified upper thoracic ventral spinal roots from the Atacama desert[a] 3000 years old from which single fascicles were placed on gelatin coated microscope slides were examined by standard immunohistochemical methods. Some nerves were also examined histologically and by electron microscopy. Nerve fibers were separated from the epineurium of 19 naturally mummified sural nerves from the Atacama desert[a] 1000–2000 years old for quantitation of SP- nerve:epineurium ratios by ELISA. Blood vessels were teased from the superficial subcutaneum of 3 naturally mummified samples of forearm skin from the Atacama desert[a] 3000 years old and stained with methylene blue. Two naturally mummified intracardiac tissues from the Atacama desert[a] 1100 years old were examined for glycosylated hemoglobin.

Results: Histology and electron microscopy of sural nerves disclosed poorly preserved fibers with occasionally recognizable myelin sheaths and better preserved ultrastructure of axons. The enteric neurons and fibers showed immunoreactivity for 5-HT, PYY and NOS. Ventral spinal roots revealed a loss of NOS and Met-enkephalin containing varicose fibers and stained positively for PGP 9.5. SP-nerve:epineurium ratios was 1.3Å0.3 (contemporaneous normal 5) but in one [a]2000 year old sural nerve the ratio was 4.9. Perivascular cutaneous nerve fibers were abundantly stained with methylene blue in all samples examined. The tissues from heart chambers showed 5% hemoglobin A1C (contemporaneous normal 4.2–6.4%) of total hemoglobin.

Conclusion: The preservation of neurochemicals in nervous tissue for millennia suggests that the possibility of determining the presence of diabetes mellitus in pre-Inca civilizations may allow better understanding of the disease in contemporaneous Native Americans.

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Acknowledgments: Tissues were generously donated by: Sonia Guillen PhD, Peru; Calogero Santoro, PhD, Chile, and Arthur Aufderheide, MD, USA. Support: NMHEMC Research Foundation; NIH grant-in-aid IHSEP-02.

Effects of central A2 receptors on aortic baroreceptor and cardiopulmonary receptor reflexes in anaesthetized rabbits

Philip A. Carey, David Jordan

Autonomic Neuroscience Institute and Department of Physiology, Royal Free and University College Medical School, Royal Free Campus, Rowland Hill Street, London, UK

Activating central A2 adenosine receptors produces potent cardiovascular responses in vivo (Barraco & Phillis, 1991). Since the nucleus tractus solitarius (NTS), where sensory afferents terminate, contains A2 binding sites (Castillo-Melendez et al, 1994), A2 receptors may modulate effectiveness of cardiovascular reflexes. We have investigated the effects of a selective A2 receptor agonist, 5′-(N-Cyclopropyl)-carboxamidoadenosine (CPCA) on responses evoked by activating aortic baroreceptor and cardiopulmonary receptor afferents.

New Zealand White rabbits (2.3–3.0 kg) were anaesthetized with urethane (1.5 g kg-1 i.v.), pretreated with atenolol (1 mg kg-1) and allowed to breathe O2-enriched air. Recordings of baseline and reflexly-evoked changes in mean arterial blood pressure (MAP), ECG, renal (RNA) and phrenic (PNA) nerve activities were made. Aortic baroreceptor afferents were activated by electrical stimulation of the left aortic nerve for 5 s (5–160Hz, 1ms, 6–7.5V). Cardiopulmonary afferents were activated by injection of phenylbiguanide (PBG, 15–40μg kg-1) into the right atrium. CPCA was administered intracisternally (20 μl over 20 s) via a cannula inserted into the exposed atlanto-occipital membrane. The effects of CPCA injection on the reflex changes were compared with time-matched vehicle controls by using two-way analysis of variance. The means were compared using the least significance difference test. All values are represented as mean ± S.E.M.

Administration of CPCA (15–20 nmoles kg-1) produced transient decreases only in MAP and R-R interval. The reflex hypotension evoked by cardiopulmonary afferent stimulation was significantly reduced within 5 mins of CPCA injection by 10.8 ± 1.5 mm Hg ($p < 0.01$ vs time-matched control). In addition, the reflex increase in R-R interval was potentiated by CPCA (57.8 ± 18.8ms), and this became significant at 20 mins. At 160Hz the aortic nerve evoked hypotension was significantly reduced by CPCA after 5 mins (11.5 ± 4.5 mmHg). Although at the same time the reflex increase in R-R interval tended to be potentiated (16.3 ± 4.9 ms), the changes did not reach significance ($p > 0.05$).

These data demonstrate that activation of central A2 receptors can modulate the effectiveness of both aortic baroreceptor and cardiopulmonary reflexes. Furthermore, there appears to be a preferential effect on the reflex hypotension compared the bradycardia.

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Presynaptic 5-HT3 receptors mediate an excitatory action of 5-HT on dorsal vagal preganglionic neurones in rat: an in vivo iontophoretic study

Yun Wang, Andrew G. Ramage, David Jordan*
Departments of Pharmacology and *Physiology, Autonomic Neuroscience Institute, Royal Free and University College Medical School, Royal Free Campus, Rowland Hill St., London, UK

Iontophoretic application of 5-HT excites dorsal vagal preganglionic neurones (DVPNs) in anaesthetized rats (Wang et al., 1995). Since autoradiographic binding studies have localised 5-HT3 binding sites in the dorsal vagal nucleus (Leslie et al., 1994), the aim of this study was to investigate whether this excitation is mediated by 5-HT3 receptors.

Rats were anaesthetized with pentobarbitone sodium and artificially ventilated. Single-unit activity was recorded from antidromically identified DVPNs using multi-barrelled electrodes. Iontophoretic application of 5-HT at low current (<10nA) increased the activity in 46 out of 63 (73%) neurones tested. This 5-HT evoked excitation was attenuted by co-iontophoresis of 5-HT3 receptor antagonists granisetron in 8 of 11 and tropisetron in 5 of 5 DVPNs tested. Phenylbiguanide (PBG), the selective 5-HT3 receptor agonist, mimicked the effect of 5-HT, causing of excitation in 89 out of 105 (85%) DVPNs tested. PBG evoked excitation was also attenuated by granisetron (8/11) or tropisetron (2/3). Further, the PBG evoked excitation was prevented by co-iontophoresis of low current of Mg2+ (1–10nA, 16/17) or Cd2+ (2–20nA, 7/8). Mg2+, at this low current range did not affect the baseline firing rate (n = 17) or NMDA-evoked excitations (n = 8), although at a higher current (20–40 nA), Mg2+ did attenuate the NMDA evoked excitation and the baseline firing rate. This suggests that these 5-HT3 receptors are located presynaptically to the DVPNs. In addition, PBG evoked excitation was also attenuated by both NMDA and non-NMDA receptor antagonists AP-5 in 8 out of 8 and DNQX in 3 out of 3 DVPNs tested suggesting of release of glutamate.

Intracellular recordings were made from 9 DVPNs by using combined single intracellular and multibarrelled electrodes. The mean membrane potential was 58.0 ± 3.5 mV (mean ± s.e.mean). Iontophoretic application of PBG depolarised the membrane potential by 7.0 ± 3.5mV and increased the firing rate in 6 DVPNs. In the other 3 neurones, PBG increased synaptic noise and firing rate without causing any membrane potential change. These PBG evoked effects were prevented by co-ionophoresis of Mg2+ in all 6 neurones tested.

It is concluded that activation of 5-HT3 receptors localized presynaptically in the dorsal vagal motor nucleus increases the release of glutamate, which excites the DVPNs by acting on both NMDA and non-NMDA receptors.

Supported by the British Heart Foundation and Wellcome Trust.

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Effect of antagonism of central 5-HT1A receptors on baroreceptor and cardiopulmonary receptor reflexes in anaesthetized rabbits.

Matthew R. Skinner, Andrew G. Ramage*, David Jordan
Autonomic Neuroscience Institute, Departments of Physiology and *Pharmacology, Royal Free and University College Medical School, Royal Free Campus, Rowland Hill Street, London, UK

Activation of central 5-HT1A receptors in anaesthetized rabbits potentiates the reflex excitation of cardiac vagal outflow produced by stimulating cardiopulmonary or baroreceptor afferents (Skinner et al. 1997a). These effects can be prevented by prior administration of WAY-100635, a selective 5-HT1A receptor antagonist (Skinner et al. 1997b). The present study was carried out to determine if there is ongoing modulation of these reflexes by 5-HT 1A receptors.

Male rabbits (2.0–3.5 kg) were anaesthetized with urethane (1.5 g kg-1; i.v.), pretreated with atenolol (1mg kg-1; i.v.) and allowed to breathe O2-enriched air. Recordings were made of arterial blood pressure, renal (RNA) and phrenic nerve activities (PNA). ECG was recorded, from which changes in R-R interval were measured. Aortic baroreceptor afferents were activated by electrical stimulation of the left aortic nerve (1ms, 5–7V, 160Hz, 5s) or cardiopulmonary afferents were activated by right atrial injection of phenylbiguanide (PBG, 7–40 mg kg-1). When three stable control reflexes had been recorded, either saline or WAY-100635 was administered i.c. (20 ml over 20 s) and the stimuli repeated (aortic nerve at 3.5 min; PBG at 5 min). The effect of WAY-100635 (n = 5) on the reflex responses were compared with that of saline by two-way ANOVA. The least significant difference test was used to compare the means. All values are means ± sem.

WAY-100635 caused a significant ($P < 0.01$) increase in baseline RNA after 3.5 min and a fall in blood pressure after 10 min. but had no effect on R-R interval or PNA. The aortic nerve evoked increase in R-R interval was significantly ($P < 0.01$) reduced 3.5 min after WAY-100635 by 24 ± 5 ms compared with 0 ± 4 ms after saline and at this time the reflex decrease in blood pressure was significantly reduced by 14 ± 2 mmHg compared with an increase of 2 ± 2 mmHg after saline. Similarly, 5 min after the injection WAY-100635, the increase in R-R interval evoked by cardiopulmonary afferents was significantly reduced by 46 ± 6 ms compared to an increase of 3 ± 2 ms after saline. At the same time, the reflex decrease in blood pressure and the reflex increase in PNA were also significantly reduced by 22 ± 4 mmHg and 16 ± 8 bursts min-1 compared to 1 ± 1 mmHg and 1 ± 2 bursts min-1 respectively, after saline.

These data demonstrate that central 5-HT 1A receptors tonically modulate baroreceptor and cardiopulmonary reflex activation of cardiac vagal outflow in anaesthetized rabbits.

M.R.S. is a British Heart Foundation PhD student.

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Calretinin-immunohistochemistry characterizes vagal-afferent nerve fibers in the rat esophagus

M. Dütsch*†, J. Wörl†, U. Eichhorn†, M. Kressel†, W.L. Neuhuber†
Department of Anatomy I† and Department of Neurology*, Friedrich-Alexander-University, Erlangen-Nuremberg, Germany

Background: Calretinin-immunoreactivity (CR-IR) has been reported in cranial sensory and dorsal root ganglia (DRG) neurons. This study was designed to test whether CR-IR specifically characterizes vagal afferents in the rat esophagus as previously suggested for the Calcium-binding protein Calbindin (1).
Methods: We used immunocytochemistry combined with retrograde fluorogold-tracing and confocal laserscanning-microscopy.
Results: Calretinin-immunoreactive thick fibers and their endings on myenteric ganglia showed the morphology of intraganglionic laminar endings (IGLEs). Very few myenteric neurons were calretinin-immunoreactive. Only fine varicose fibers originated from them. More than 80% of nodose ganglion neurons retrogradely

labeled from the cervical esophagus showed CR-IR. Nodose ganglion neurons innervating the abdominal esophagus were less frequently calretinin-immunoreactive. Retrogradely labeled DRG cells did not display any calretinin-immunoreactivity. Co-localization of Calretinin and CGRP or NADPH-diaphorase in fibers and neurons of the esophagus and DRG was rarely observed. About 75% of large and about 10% of small DRG neurons displayed Carboanhydrase-histochemistry and CR-IR. However, Carboanhydrase and Calretinin did not co-exist in esophageal structures.

Conclusion: Results of retrograde tracing and comparison of CR-IR with CGRP-, Carboanhydrase- and NADPH-diaphorase-histochemistry in the esophagus and DRG support the hypothesis that Calretinin-immunoreactive IGLEs originate from nodosal neurons. Calretinin may be used as an immunohistochemical marker for vagal afferents, especially in the cervical rat esophagus.

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Quantitative sudomotor axon reflex test (QSART): a new possibility to test distal sites

A. Riedel*, S. Braune*, G. Kerum†, C.H. Lücking*
*Department of Neurology, University of Freiburg, Germany
†Department of Internal Medicine, University of Freiburg, Germany

The Quantitative Sudomotor Axon Reflex Test (QSART) quantifies the response of postganglionic sympathetic sudomotor efferents, which are activated via an axon reflex by the controlled iontophoretic stimulation with acetylcholine. Testing of axon reflex sweating is an established tool in the evaluation of C-fibre-function in diabetic neuropathy. Previously we introduced a newly designed capsule for the distal performance of a QSART, which allows the measurement at fingers and toes.[1]

In this study we compared 20 healthy male volunteers with 15 male patients suffering from diabetes with complaints suggestive of small fibre neuropathy but with normal sensory nerve conduction studies of the upper and lower limbs. A QSART was performed at the forearm, at the thumb and at both lower legs over the distal part of the tibialis anterior muscle.

There were no significant differences for the sweat volume at the forearm and the lower legs between the groups. Also no significant differences of sweat response latencies were found between the groups at all sites tested. Sweat volume at the thumb was significantly lower in the patient group ($p < 0.0024$).

Like in previous studies[2] a high inter-individual variation of the QSART-response was found in the control group. This can make it difficult to distinguish pathological absolute values from normal values. The calculation of the forearm/finger ratio minimises this problem since it has a low standard deviation in male healthy volunteers compared to the absolute values of the sweat volume. Due to this fact the forearm/finger ratio showed the most significant difference between the groups ($p < 0.0007$).

Despite the fact that all patients reported symptoms of small fibre neuropathy only 3 patients had a result below the 5th percentile of the normal control group concerning the sweat volume at the forearm. Four patients showed a result below the 5th percentile of the normal control group in the sweat volume at the thumb. Seven patients showed a result below the 5th percentile of the normal control group in the forearm/finger ratio.

We conclude that the distal measuring device and the forearm/finger ratio are more sensitive tools in the early detection of distally beginning neuropathies in comparison to the commonly used proximal testing sites.

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Orthostatic hypotension and its symptoms in familial amyloid polyneuropathy

A.E. Jeeves, C.J. Mathias
Neurovascular Medicine Unit, Division of Neuroscience and Psychological Medicine, Imperial College Medical School at St Mary's London; Autonomic Unit, University Department of Clinical Neurology, National Hospital for Neurology and Neurosurgery, Queen Square & Institiute of Neurology, University College London

Familal amyloid polyneuropathy type I is an inherited neurodegenerative disorder associated with mutations in the plasma protein transthyretin. Dysfunction of both the parasympathetic and sympathetic system have been documented in FAP, which are attributable to protein deposition and nerve fibre changes in the autonomic nervous system [1]. An early report suggested a dissociation between symptoms and signs of orthostatic hypotension (OH) [2]. We now report the results of physiological investigations in a larger group, constisting of 35 patients, 18 with the met30 mutation (met30 age range 20–58, mean duration symptoms 3.5 years) and 17 with 8 other miscellaneous transthyretin mutations (misc 29–68, duration 3.3 yrs). Autonomic testing was as previously described [3] and symptoms were elucidated from questionnares and case notes. Orthostatic hypotension was defined as a systolic fall of greater than 20 mmHg or a diastolic fall of greater than 10 mmHg.

Posturally-related dizziness occurred to a similar extent in both groups (6 (33%) met30 vs 5 (29%) misc), as did visual disturbances: 5 (22%) met 30 vs 3 (18%) misc. One patient in each group (6%) reported syncope and coathanger pain. Oliguria was unreported; nocturia occurred in 3 (17%) met30 and 5 (29%) misc.

The mean supine BP was lower in the met30 group (Table). All met30 had impaired pressor responses, compared with 13 (76%) misc. Cardiac parasympathetic dysfunction was present in 17 (94%) met30 and 12 (71%) misc. OH occurred, 2 (11%) of the met30 vs 7 (41%) misc on 45° tilt. On standing, 7 (41%) met30 patients and 5 (33%) misc had OH.

Mean values and standard error for supine and 45° tilt blood pressure and heart rate

	Supine		
	Systolic BP	Diastolic BP	Heat rate
met30	111 ± 3	71 ± 3	84 ± 3
misc	121 ± 4	79 ± 3	73 ± 4
	45° tilt		
	Systolic BP	Diastolic BP	Heat rate
met30	104 ± 3	70 ± 3	93 ± 4
misc	108 ± 6	72 ± 4	78 ± 4

We conclude that orthostatic dizziness and OH correlate in met30 (33% vs 39%), but there is a dissociation in the other phenotypes (misc 29% vs 59%). Symptoms of OH such as visual disturbances, syncope and coathanger pain are infrequent and occur in similar proportions in each group. Autonomic function, however, was abnormal in the majority of both groups. Therefore, cardiovascular autonomic function should be determined in FAP patients regardless of a lack of characteristic orthostatic features. This is particularly important in the management of patients that undergo therapeutic orthotopic liver transplantation.

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Peripheral vasoconstriction following electrical stimulation refines the diagnosis of peripheral diabetic autonomic neuropathy

M. Hecht, M.J. Hilz, R. Freeman*, W. Singer, C. Kölsch, B. Neundörfer

Depts. of Neurology, University of Erlangen-Nuremberg, Germany, and *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Arousal induced sympathetic skin response (SSR) is often used to assess peripheral diabetic autonomic neuropathy. However, the method is coarse and hardly quantifies autonomic dysfunction. Arousal should induce a sympathetically mediated peripheral vasoconstriction.

In this study, we evaluated whether electrically induced arousal is followed by a change of peripheral skin blood flow (SBF), and whether this change is reduced in diabetic patients.

In 14 controls and 14 diabetic patients (3 IDDM,11 NIDDM), SBF at the index finger pulp was monitored at rest and after electrical stimulation of the contralateral wrist (0.1 msec, 100–250 V) using a Perimed TM laser Doppler. Simultaneously, SSR was recorded from the ipsilateral palm according to standard techniques.

SSR was positive in all study participants. In controls, SBF decreased on an average by 42% (SD ± 25%) with a stimulus latency of 6–14s. In diabetics, arousal induced SBF decrease was significantly smaller (24% ± 31%) than in controls (Mann-Whitney: $p < 0.05$). In seven patients, there was no change of SBF despite preserved SSR.

Laser Doppler measurement of SBF after electrically induced arousal quantifies impairment of peripheral sympathetic vasoinnervation in diabetic patients and is better suited for an early diagnosis of autonomic dysfunction than is SSR recording.

Erythropoietin responsive anaemia in diabetic autonomic neuropathy

A.S. Winkler, J. Marsden, P.J. Watkins, K.R. Chaudhuri

Clinical Neurosciences and Diabetes Centre, King's College Hospital

Background: We previously studied 15 insulin dependent diabetics with florid autonomic neuropathy (IDDM-DAN) and found that 11 of these patients were anaemic due to erythropoietin (EPO) depletion. Other causes of anaemia were excluded and creatinine was not exceeding 122 μmol/L.

Methods: Four anaemic IDDM-DAN patients were treated with EPO (sex: all female; age: 48, 41, 30 and 51 yr.; duration of disease: 13, 24, 19 and 37 yr.). They all presented with significant postural hypotension (systolic blood pressure drop > 20 mmHg) and at least one other symptom of diabetic autonomic neuropathy. Autonomic function tests were grossly abnormal. EPO was injected 3 times a week in a dose of 25 IU/kg BW for at least three months. Patients then were taken off treatment for 3 months and subsequently put back onto treatment and followed up for another 3 months. Haemoglobin (Hb) was measured bimonthly in all the patients.

Results: Hb before treatment was 11.6, 9.9, 10.0 and 10.1 g/dL in patient 1 to 4. It steadily increased up to 14.0, 12.4 and 13.9 g/dL in patient 1, 3 and 4 after three months on treatment and up to 13.1 g/dL in patient 2 after four months on treatment. After withdrawal of EPO the Hb gradually decreased and was 10.8, 10.5 and 9.9 g/dL in patient 2, 3 and 4 after three months off treatment. During the second treatment phase the increase in Hb was reproducible when compared to the first treatment period. Patient 1 dropped out of the study after three months on EPO.

Conclusion: Some IDDM-DAN patients present with a normochromic anaemia which requires treatment with EPO.

Cardiac sympathetic denervation in Ross syndrome demonstrated by MIBG-SPECT

B. Neundörfer[1], K. Kirchberger[1], C. Koelsch[1], G. Platsch[2], M.J. Hilz[1,3]

Depts. of Neurology[1] & Nuclear Medicine[2], University of Erlangen-Nuernberg, Germany; Dept. of Neurology[3] New York University, New York, NY, USA

Ross syndrome is a rare degenerative disease defined by the triad of tonic pupil, hyporeflexia and segmental anhidrosis. Presumably, the syndrome is due to postganglionic parasympathetic and sympathetic lesions. Cardiovascular dysfunctions include orthostatic dysregulation and reduced heart rate variability.

We report the case of a 55-year-old man with Ross syndrome, in whom we studied cardiac sympathetic innervation by means of I-123 metaiodobenzylguanidine single photon emission computed tomography (MIBG-SPECT).

The patient manifested with anisocoria (right 5.8 mm, left 4.8 mm), blurred vision on accommodation, complete anhidrosis apart from excessive perspiration in the right groin and left axilla. Direct light reflex was absent on the right and sluggish on the left pupil. Pupillary accommodation response was positive. 0.1% pilocarpine induced brisk pupillary constriction. Laboratory parameters, cerebrospinal fluid, cranial and spinal computed tomography, MRI, and neurophysiological tests were normal. Only sympathetic skin responses and quantitative sudomotor axon reflex tests were negative on the right palm and on both soles. Thermoregulatory sweating was preserved only in the right groin and left axilla. Heart rate variability and blood pressure were normal at rest and during challenge maneuvers. Cardiac sympathetic innervation was assessed by MIBG-SPECT. Posterolateral cardiac uptake of the norepinephrine analogon MIBG was significantly reduced, global myocardial MIBG uptake was slightly decreased, the inhomogeneity index was increased, all indicating postganglionic sympathetic cardiac denervation. Normal myocardial perfusion scintigraphy (Tc-99m-Sestamibi-SPECT, MIBI) ruled out ischemic cardiac lesions.

Apart from pupillary and sweating tests, extensive neurophysiological and autonomic testing showed normal results in this patient. Only MIBG-SPECT demonstrated cardiac sympathetic dysfunction. MIBG-SPECT is helpful to identify—even subclinical—sympathetic cardiac denervation and to further clarify the pathology of Ross syndrome.

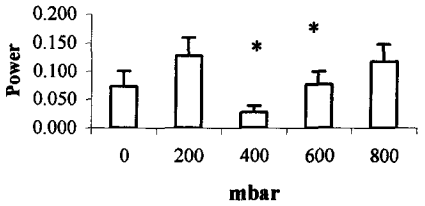
Influences of antigravity muscles on the cardiovascular system

J.O. Fortrat, G. Demond, M.A. Custaud, C. Gharib

Laboratoire de Physiologie de l'Environnement, Lyon cedex, France

It has been recently suggested that a change in the relationships between the equilibrium and the cardiovascular functions could be involved in the orthostatic hypotension observed after actual or simulated weightlessness. The vestibular influences on the cardiovascular system are clear (1) but equilibrium involves other mechanisms. Some studies on anaesthetised animals demonstrated that the stimulation of the muscular mechanoreceptors by exercise could influence the cardiovascular system (2). In order to determine if

the antigravity muscles could influence the cardiovascular system in humans, we led a pilot study on 8 healthy volunteers. Both legs of the supine subjects (quadriceps area) were slightly compressed at a pressure of 0, 200, 400, 600 and 800 mbar on 7 cm^2. Each step was 5 min long and was followed by a recovery of 5 min. The steps were randomly arranged. The beat-by-beat RR-interval and Finapres systolic blood pressure were continuously recorded during the experiment. The data from each step were subjected to coarse graining spectral analysis to obtain the low, high and total frequency power (absolute and normalised) and the low/high frequency ratio. Our results show that only the normalised high frequency power of systolic blood pressure was significantly altered by muscular compressions (Figure).



Effect of muscular compressions (x-axis) on the normalised high frequency power of systolic blood pressure (y-axis; * $p \leq 0.05$ vs 200 mbar).

Despite the limitations of this pilot study we conclude that i) slight compressions of muscles involved in the equilibrium have a small effect on the cardiovascular system ii) the optimal muscular compression for further studies is 400 mbar on 7 cm^2.

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The effect of age and gender on growth hormone stimulation by i.v. clonidine in normal man

M. Sivanandan, J. Kimber, L. Watson, C.J. Mathias
Neurovascular Medicine Unit Department of Neuroendocrinology, Division of Neuroscience and Psychological Medicine, Imperial College Medical School at St Mary's Hospital, London
Autonomic Unit, University Department of Clinical Neurology, National Hospital for Neurology and Neurosurgery Queen Square & Institute of Neurology, University College London.

The central α_2-adrenoceptor agonist clonidine, stimulates growth hormone (GH) secretion in normal man, unlike patients with Multiple System Atrophy (MSA) [1]; it is also used intravenously to distinguish these patients from idiopathic Parkinson's disease without autonomic failure [2]. Both age [4] and sex [5] related changes in the GH response to clonidine in normal subjects have previously been observed using oral clonidine. The age and gender effects of i.v clonidine, which results in higher CNS levels of the drug, are not known. This was therefore studied in 83 healthy normal subjects age 19–89, M:F approx 1.2:1. Subjects were divided into 6 age groups, <25, 25–35, 36–45, 46–55, 56–64, 65+. After an overnight fast, subjects were studied after 30 mins supine rest. Antecubital vein cannulation was performed for administration of clonidine (2(g.kg) and collection of blood samples for measurement of serum GH, plasma catecholamines and glucose. Sampling was performed at 15 min intervals for 60 mins. Basal levels of GH showed no differences with age or sex. A significant rise in GH was observed in all age groups. Males showed an age-sensitive response; this was greatest in the 25–35 group and then declined with age. No sex related differences in stimulated GH levels were detected in >45 groups. Basal noradrenaline levels showed a trend to higher values with increasing age, but this was not statistically different. Following clonidine, a similar percentage fall in plasma noradrenaline was observed in all age groups, without a gender effect. Plasma glucose showed no significant differences before or after glucose. We conclude that i.v clonidine raises GH significantly in all age groups. The GH responses indicated a sexually dimorphic pattern <45years; this did not occur in those >45, although there was an age related decline in both sexes. Thus in older patients with MSA/IPD (usually>55) age and sex differences should not affect the clonidine-GH response.

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Effect of salt loading on blood pressure and blood pressure control

V.L. Wight, R. Hainsworth
Institute for Cardiovascular Research, University of Leeds, UK

Introduction: Salt loading may be effective in the treatment of orthostatically related syncope. However, since high levels of dietary salt are associated with hypertension we undertook this study to examine the effects of salt on supine and tilted blood pressures in patients complaining of syncope.
Methods: Seventy patients with histories suggestive of orthostatic hypotension and 24 hour urinary sodium excretions less than 170 mmol, underwent a combined tilt and lower body suction test. Blood pressure was recorded throughout the test at 2 minute intervals and orthostatic tolerance was taken as the time to presyncope. Patients were then instructed to take 120 mmol slow sodium per day and were retested after 3 months.
Results: Forty-nine patients (70%) showed increases in orthostatic tolerance of 2 minutes or more (responders); 30% were either unchanged or showed decreased tolerance (non-responders). The effects of salt on supine and tilted blood pressures are summarised in the table.

	Supine baseline	Supine after salt
Responders	110.7 ± 2.2/ 63.2 ± 1.5	113.2 ± 2.6/ 65 ± 1.7
Non-responders	112.6 ± 4.0/ 62.9 ± 2.3	120.1 ± 4.3**/ 66 ± 2.9*
	Tilt baseline	**Tilt after salt**
Responders	114.1 ± 1.9/ 73.2 ± 1.3	122.0 ± 2.8**/ 76.6 ± 2.2*
Non-responders	114.7 ± 4.0/ 74.0 ± 3.5	122.5 ± 4.8* 80.5 ± 3.0*

Supine and tilted systolic and diastolic blood pressures before and after salt loading in responders and non-responders. Values significantly different from those before salt: *P < 0.05, **P < 0.01.

In the responders, salt did not significantly change supine blood pressures, but pressures during tilt were significantly greater (systolic / diastolic: P < 0.01 / 0.05). In the non-responders, however, both supine and tilted pressure were significantly increased after salt.
Conclusion: Salt loading is an effective treatment in 70% of patients with poor orthostatic tolerance and does not have a significant effect on supine blood pressure in these patients. However, in the 30% who do not show improvement to salt loading there are increases in supine blood pressure. These results imply that patients

should be assessed after salt loading and that this treatment should be continued only in patients shown to respond.

Continuous haemodynamic monitoring in swallow-induced syncope

Kazushi Deguchi, Christopher J. Mathias
Autonomic Unit, University Department of Clinical Neurology, National Hospital for Neurology & Neurosurgery, Queen Square & Institute of Neurology, University College London and Neurovascular Medicine Unit, Division of Neuroscience & Psychological Medicine, Imperial College School of Medicine at St Mary's, London, UK

There have been no previous observations on continuous haemodynamic recordings, including various cardiovascular derivatives, before, during and after swallow-induced syncope. We describe a 69 year old man with a 12 year history of intermittent syncope associated with swallowing solid food mainly after having fasted. He was on enalapril, propranolol, bendrofluazide, omeprazole, finasteride and aspirin. Detailed investigations, including gastro-intestinal evaluation, measurement of various gut hormones and autonomic testing, indicated no abnormality. A liquid food meal, performed before fasting, failed to elicit an episode; after fasting a liquid meal caused a small fall in blood pressure, from which he rapidly recovered. A solid meal (egg sandwiches), however, after an overnight fast provoked a typical attack. Continuous haemodynamic monitoring (with a Portapres II) indicated an initial rise in blood pressure, cardiac output and then heart rate with facial flushing, sweating and bulbar conjunctival injection. This was followed after 2 minutes by a progressive fall in blood pressure, stroke volume, and then cardiac output. Heart rate continued to rise for a further 2 minutes and then fell from a maximum of 108 beats/min to 58 beats/min. He had blurred vision, became confused and was noted to have facial pallor. He was near collapse and was laid horizontal on his side, when he vomitted clear fluid. The blood pressure slowly recovered and remained low over 48 minutes of observation. This favoured an initial increase in sympathetic activity, followed by vasodepression that could have been caused by withdrawal of sympathetic neural activity, or activation of vasodilatatory mechanisms. The reduction in cardiac filling then may have stimulated cardiac ventricular mechanoreceptors and a Bezold-Jarisch reflex, and caused bradycardia. Thus, unlike previous reports, the key factor was vasodilatation and not bradycardia. Because the attack appeared to begin after enalapril was started, this drug was withdrawn. Following this there were no further episodes, although rechallenge induced a further attack after eating breakfast. Enalapril therefore, by mechanisms that are unclear, may have contributed to his swallow-induced syncope.

Pupil abnormality in autonomic neuropathy

S.E. Smith
Department of Neuro-Ophthalmology, National Hospital for Neurology & Neurosurgery, Queen Square, London, UK

Pupil abnormality may be hard to detect in patients with generalised autonomic neuropathy for several reasons. First, the signs are bilateral and therefore no normal pupil exists for comparison. Secondly, there is wide variability in pupil diameter and reactivity to light and near within the normal population. Thirdly, in some types of autonomic neuropathy the pupils are normal despite widespread autonomic abnormality elsewhere in the body. Fourthly, eyedrop testing for receptor supersensitivity is unsound because of the dry eyes present in many of the patients. Pupil signs in 87 patients with generalised autonomic neuropathy of various origins are presented, using light reflex responsiveness to indicate parasympathetic and redilatation velocity to indicate sympathetic function. Abnormalities were present in all patients with amyloidosis (n = 10) and in most patients with pure autonomic failure (n = 13) and diabetes (n = 21). By comparison, pupils were abnormal in only one of 29 patients with multiple system atrophy and in none of 5 with HIV-related autonomic neuropathy. The pupils were abnormal in 2 siblings with dopamine hydroxylase deficiency and in single patients with Riley Day syndrome, familial dysautonomia, HSAN type III, Anderson-Fabry disease and Eaton-Lambert syndrome. The significance of these findings is discussed.

Cutaneous vasodilater responses to sodium nitroprusside but not those to acetylcholine may be impaired in patients with primary Raynaud's disease

Clare M. Edwards, Janice M. Marshall
Department of Physiology, The Medical School, Birmingham, UK

In previous studies, we showed that central neural control of the cardiovascular system may be different in patients with Primary Raynaud's Disease than controls, in that both the cutaneous vasoconstrictor and muscle vasodilator responses to the acute emotional stress of sound, or mild cooling persist on repetition of the stimulus in Primary Raynaud's patients, but habituate in controls. Further, Primary Raynaud's patients show an accentuated release of Endothelin-1 in response to mild cooling of the hand (1,2). We have now studied whether the vasodilator role of nitric oxide (NO) is changed in Primary Raynaud's Disease. In 12 Primary Raynaud's patients and in 12 matched controls, cutaneous red cell flux was recorded from the middle digit of the left hand before and during microiontophoresis of the NO donor, sodium nitroprusside (SNP), acetylcholine (ACh) or their vehicles. Cumulative dose-response curves were obtained by applying SNP at 5 × 20s pulses at 0.1 mA, then 1 × 20s pulse at 0.2 mA, with 180s intervals between pulses, or acetylcholine (ACh) at 6 × 20s pulses at 0.1 mA, then 1 × 20s pulse at 0.2 mA at 60s intervals. Arterial pressure was recorded using the Finapres and digital cutaneous vascular conductance (DCVC) was calculated. Neither vehicle had a significant effect in Primary Raynaud's patients, or controls, but we expressed changes in DCVC as drug minus vehicle response. ACh produced comparable graded increases in DCVC in both Primary Raynaud's patients and controls with no significant difference between the two groups. By contrast, Primary Raynaud's patients showed substantially smaller increases in DCVC to SNP than controls, ($P < 0.01$ by ANOVA) These results suggest that dilator responses to NO are attenuated in Primary Raynaud's Disease, while the apparently normal dilator responses to ACh suggest that the reduced effect of NO may be compensated for by the action of other dilator substances. We propose that reduced sensitivity to NO, together with accentuated release of the vasoconstrictor Endothelin and persistence of neurally-mediated cutaneous vasoconstrictor responses to cooling or emotional stress, all contribute to the genesis of vasospasm in Primary Raynaud's Disease.

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Orthostatic intolerance and syncope

Alfonso Lagi, Carlo Tamburini, Lamberto Fattorini, Simone Cencetti
Autonomic Unit, Department of Internal Medicine
Santa Maria Nuova Hospital, Florence, Italy

Introduction: The autonomic nervous system has an important role in the vaso-vagal syncope (VVS). Its influence is before and during the syncopal crisis characterised by a reduction of the sympathetic function and increase of vagal activity as on the heart and the vessels of resistance (Morillo CACirculation 1997). We discuss

the influence of the autonomic nervous system before the crisis. We think that some subjects could be prone to syncope because they have an abnormal balance between sympathetic and parasympathetic system.

Methods: We studied 42 patients (27 females, mean age 29 yo) suffering from VVS (more than three episodes in the last ten years) and 19 controls (10 females, mean age 27 yo). The patients were observed in the Emergency Room, all referred to a recent episode of VVS, excluding those who had been in crisis for more than 24 hours. They were studied with a 24-hour ECG recording (Remco–Milano) and head up tilt (HUT) test (at 60° for 45') during the following 24 hours. During HUT, ECG was recorded continuously and arterial pressure was monitored beat by beat (Finapres–Omheda). On the 24-hour ECG recording Mean Heart Rate (HR), as R-R interval, Standard Deviation (sd) and pNN50 and rMSSD were considered as an index of autonomic function, specifically of vagal activity; on HUT, mean RR interval and Systolic and Diastolic arterial Pressure (PaS and PaD) were considered, in clinostatism (HUT-0) and in the first three minutes of orthostatism (HUT-I and HUT-3). Subsequently, the patients were subdivided in two subgroups as the results of pNN50 and rMSSD showed, considering the value of the control subjects.

The data were analysed with the Student's t test for paired data and the level of 0.05 was chosen as significant.

Results: No significant differences were found between VVS and controls (Tab 1) except the values of the vagal markers: pNN50 and rMSSD.

Consequently we evaluated the data of the patients according to the mean value of pNN50 and rMSSD plus the standard deviation (Tab 2).

The two populations of patients with VVS had the same values of HR, PaS and PaD in clinostatism but they differed in orthostatism for the three parameters studied. In the group with reduction of vagal markers (PNN50 and rMSSD) we observed an increase of HR and a reduction of PaS and PaD: this difference is more evident at HUT-3.

Conclusion: This report offers new insight demonstrating that there is a difference among the population of VVS patients due to the different behaviour in orthostatism which may be linked to a different vagal modulation. An explanation of these results may come from the hypothesis that the VVS patients with reduction of vagal tone and arterial pressure and increase of HR may be affected by orthostatic intolerance.

Table 1. Results of the parameters evaluated in study: VVS vs Controls

	VVS—42 pts	Controls—19 subjects
mean age (y.o.)	29	27
Heart rate—RR intervals (ms)	890 (67')	910 (66')
Standard deviation (ms)	70	80
pNN50 (%)	8.5 (2.1)	30.2 (6.1)**
rMSSD (ms)	21.1 (2.1)	45.9 (9.2)**
PaS (mmHg)	121 (4)	122 (4)
PaD (mmHg)	72 (3)	71 (2)

Table 2. Differences between the two groups of patients with VVS

	VVS − pNN50 < 11%; rMSSD < 24 ms		
mean age	27		
	HUT-0	HUT-1	HUT-3
HR ms	870 (69')	701 (86')*	650 (93')**
sd	50	45	40
PaS mmHg	119 (4)	104 (6)**	102 (3)**
PaD mmHg	70 (3)	69 (4)*	68 (2)**
	VVS − pNN50 > 11%; rMSSD > 24 ms		
mean age	31		
	HUT-0	HUT-1	HUT-3
HR ms	880 (68')	821 (73')	808 (74')
sd	100	80	78
PaS mmHg	123 (4)	121 (5)	120 (3)
PaD mmHg	71 (3)	73 (2)	75 (2)

*&. **p < 0.05 and 0.01. PaS & PaD = Systolic and Diastolic arterial Pressure.

Unravelling the cause of sympathetic excitation following subarachnoid haemorrhage

Gavin Lambert[1,2], Elisabeth Gaudet[1], Celine Fassot[1], Silvana Naredi[2], Peter Friberg[2], Jean-Luc Elghozi[1]

[1]Faculty of Medicine Necker, Paris, France and [2]Sahlgrenska Hospital, Gothenburg University, Gothenburg, Sweden

Using isotope dilution methodology we estimated sympathetic nervous activity in 18 patients following non-traumatic subarachnoid haemorrhage (SAH). Resting rates of noradrenaline spillover to plasma were over three times that of healthy subjects! Scientific investigations in such patients are restricted and the treatment of this condition remains one of the major focuses of neurosurgery. In response to this challenge we developed an animal model of this condition. In conscious rats, SAH was induced by injecting 150μl of homologous blood via a catheter, previously placed along the lateral surface of the brain. Control animals received saline instead of blood. Blood pressure (BP), heart rate and arterial plasma noradrenaline levels were monitored throughout the experimental period. Following induction of SAH, and indicative of pronounced sympathoexcitation, the mid frequency (MF) components of systolic BP were elevated 3 hours after the insult (10.9 ± 2.9 vs 2.9 ± 0.6 $mmHg^2$). Parallel changes in plasma noradrenaline concentration also occurred. The injection of saline into the brain did not modify BP variability. Intra-peritoneal injection of losartan following SAH-induced sympathetic activation resulted in a dramatic reduction in BP. Losartan was without effect in control animals. In a separate group of rats the injury was performed after the systemic administration of bosentan, a nonpeptide ET_A and ET_B receptor antagonist. Pre-treatment with bosentan completely prevented the SAH induced sympathoexcitation. Moreover, constant infusion of a minuscule, non-depressor, dose of sodium nitroprusside also prevented the sympathoexcitation associated with experimental SAH. These results indicate that SAH elicits a pronounced elevation in sympathetic nervous activity mediated either by direct endothelin production or by a shift in the balance between endothelin-mediated vasoconstriction and nitric oxide-induced vasodilatation. Angiotensin II involvement is also implicated.

Mechanisms underlying the impairment in orthostatic tolerance after a night sleep in patients with autonomic failure

Stefano Omboni, MD, Adrianus A.J. Smit, MD, Johannes J. van Lieshout, MD, PhD, Jos J. Settels, Ir, Gerard J. Langewouters, Ir, PhD, Wouter Wieling, MD, PhD

Academic Medical Center, University of Amsterdam, Department of Internal Medicine and TNO, Biomedical Instrumentation, Amsterdam, The Netherlands, S. Gerardo Hospital, University of Milan, Instituto Scientifico Ospedale San Luca, Instituto Auxologico Italiano and Department of Internal Medicine, Milan, Italy

Objective: To assess in patients with neurogenic orthostatic hypotension (NOH) the hemodynamics underlying the reduced tolerance to standing and walking after a night sleep.

Methods: In 10 patients with NOH (6 females and 4 males, aged 33–68 yr.) of which 7 were treated with fludrocortisone and/or sleeping in 12° head-up tilt position, continuous non-invasive finger blood pressure was recorded by the Portapres device., Beat-to-beat blood pressure (BP), heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral vascular resistance (TPR), obtained by pulse contour analysis, were assessed 1) during 5 minutes of standing in the evening (10:30 p.m.) and in the morning (6:30 a.m.) and 2) during a 15 minute walk in the afternoon (4 p.m.) and in the morning (10 a.m.),

Results: On average an inverse 24-hour blood pressure profile was found, with a large diversity in blood pressure profile among patients. Supine BP values were similar but standing BP values were higher in the evening than in the next morning ($p < 0.01$). This resulted from a reduced fall in SV and CO upon standing in the evening compared to the morning, while TPR did not change. There was no relation between the reduction in body weight during the night (mean 0.9 kg, range 0.2–1.6) and in the evening-morning difference in orthostatic blood pressure fall. In 2 severely affected patients and morning-afternoon difference in walking capacity was found. In these 2 patients walking systolic BP improved due to an increased SV and thereby CO in the afternoon while TPR decreased to a similar extent. In the remaining 8 patients, in whom no difference to tolerance to walking was found, similar changes in hemodynamics were found in the morning and in the afternoon.

Conclusions: In patients with NOH, BP during orthostasis and walking is lower in the morning than in the late hours of the day. The improved tolerance to standing and walking is due to a better maintenance of SV. Redistribution of body fluid rather than nocturnal polyuria is the likely mechanism underlying the reduction in stroke volume and orthostatic tolerance after a night sleep.

Cerebral autoregulatory response to step changes in end-tidal CO_2 in patients with sympathetic failure

M.P.M. Harms*, J.W.M. Lenders†, W. Wieling*, N.H. Secher‡, J.J. van Lieshout*

Dep. of Internal Medicine, Academic Medical Center, Cardiovascular Research Institute, Amsterdam*; Dep. of Internal Medicine, University Hospital Nijmegen†; Dep. of Anaesthesia, The Copenhagen Muscle Research Centre, Rigshospitalet, Copenhagen, Denmark‡

The ability of the brain to maintain adequate arterial perfusion is a function of its capacities to autoregulate cerebral blood flow. The integrity of cerebral autoregulation in autonomic failure has been studied during orthostasis with arterial hypotension, a condition that may interfere with the lower limit of the pressure-flow relation of the human brain. A difference in dynamic autoregulatory gain was suggested recently in patients with autonomic failure studied under those conditions. The present study aimed at quantifying the cerebrovascular resistance response in the territory of the middle cerebral artery (MCA) in autonomic failure patients. Measurements were taken in the supine position avoiding major postural changes in cerebral perfusion pressure that interfere with changes in MCA diameter. We followed the MCA blood velocity responses to step changes in end-tidal CO_2 ($P_{ET}CO_2$) under normoxic conditions in the supine position in four patients (1 female, age 40–65 yr.) with sympathetic failure and four age- and gender-matched controls.

Continuous middle cerebral artery (MCA) blood velocity was measured by insonating the proximal segment of the right MCA. Mean MCA velocity (V_m) was computed as the integral of the maximal frequency shifts over one beat divided by the corresponding beat interval. $P_{ET}CO_2$ was measured by an infrared CO_2 analyser. Controlled stepwise changes in $P_{ET}CO_2$ were induced in absence of significant changes in arterial pressure confirmed by continuous finger pressure recording. $P_{ET}CO_2$ ranged from 3.67 to 8.22 kPa in patients vs. 4.84 to 7.11 kPa in controls. The range of $MCAV_m$ was larger in patients (68–161 $cm.s^{-1}$ vs. 48–109 $cm.s^{-1}$ in controls). The steady-state $MCAV_m - P_{ET}CO_2$ response in patients, expressed as the average of three runs, amounted to 31 (21–47) $cm.s^{-1}$ /kPa CO_2 vs. 18 (10–32) $cm.s^{-1}$/kPa CO_2 in controls.

These preliminary data suggest that patients with sympathetic dysfunction regulate cerebral vascular resistance in response to changes in $P_{ET}CO_2$ at an elevated autoregulatory gain.

Valsalva manoeuvre demonstrates impaired cerebrovascular autoregulation in familial dysautonomia patients

M.J. Hilz[1,2], M. Steingrueber[1], A. Hagler[1], F.B. Axelrod[2]

Dept. of Neurology[1] University of Erlangen-Nuremberg, Germany; Dept. of Neurology[2] New York University, New York, NY, USA

Familial dysautonomia (FD) patients are at risk of increased mortality even when at rest and supine. Cerebrovascular autoregulation (CA) can be assessed in supine position by means of Valsalva maneuver (VM). Normally, autoregulatory increase of midcerebral artery blood flow velocity (CBFV) exceeds concomitant blood pressure (BP) increase during late phase II and phase IV of VM (1). In this study we evaluated CA in FD patients during VM in supine position.

In 8 FD patients (mean age 28.0 ± 9.6 years) and 12 healthy controls (mean age 27.5 ± 11.3 years), heart rate (HR), mean radial artery BP and CBFV were continuously monitored in supine position at rest and during VM (40mmHg pressure for 20 sec) using a Colin Pilot tonometric BP and HR monitor and insonating the temporal window with a 2 MHz Nicolet/EME Pioneer transcranial Doppler. Two parameters derived from Tiecks et al.[(1)], CAII and CAIV, were calculated to assess CA. CAII reflects BP related autoregulatory CBFV increase in late phase II of VM. CAII = [(CBFVII late-CBFVII early)/CBFVII early]/[(BPII late-BPII early)/BPII early]. CAIV reflects BP and HR related autoregulatory CBFV increase in phase IV of VM. CAIV = (CBFVIV/HRIV/CBFVI/HRI)/(BPIV/BPI).

In FD patients, phase IV reflex bradycardia and Valsalva ratio were smaller than in controls ($p < 0.01$). At rest and during VM, BP was slightly, but not significantly higher in patients than in controls. BP response to VM did not differ between both groups. In contrast, CAII and CAIV were significantly smaller in patients than in controls (CAIIControls = 1.69; CAIIFD = 0.88; $p = 0.007$; CAIVControls = 1.27; CAIVFD = 1.03; $p = 0.02$).

VM demonstrates that CA is impaired in FD patients even in supine position. Together with other abnormalities such as reduced heart rate variability, supine arterial hypertension and reduced baroreflex buffer capacity, abnormal CA following respiratory straining might contribute to the increased mortality rate of resting FD patients.

1. Tiecks FP, Lam AM, Matta BF, Strebel S, Douville C, Newell DW. Stroke 1995;26:1386–1392.

Continuous stroke volume by modeling flow from non-invasive arterial pressure in humans under orthostatic stress

M.P.M. Harms*; K.H. Wesseling†; F. Pott‡; M. Jenstrup‡; J. van Goudoever†; N.H. Secher‡, and J.J. van Lieshout*

Dep. of Internal Medicine, Academic Medical Center, Cardiovascular Research Institute, Amsterdam*; Dep. of Anaesthesia, The Copenhagen Muscle Research Centre, Rigshospitalet, Copenhagen, Denmark‡; Netherlands Organization for Applied Scientific Research, TNO Biomedical Instrumentation, Amsterdam†

The relationship between aortic flow and pressure can be described by a three-element model of the arterial input impedance. We computed aortic flow from arterial pressure by simulating this model, with continuous correction for variations in diameter and compliance of the aorta and investigated if under orthostatic stress, flow may still be derived from non-invasive arterial pressure.

In 10 young adults stroke volume was computed from intra-brachial (IAP) and non-invasive finger (FINAP) pressure using the Modelflow (MFSV) method. For comparison, computer controlled series of four thermodilution estimates (TDSV) were averaged during supine (SUP), standing (STD), head-down (HDT20) and head-up (HUT30 and HUT70) tilted position.

TDSV ranged from 33 to 137 ml. The difference for the pooled data between TDSV and $MFSV_{FINAP}$ (range −16 to 33 ml; n.s.) was smaller than the difference between TDSV and $MFSV_{IAP}$ (range −16 to 51 ml; $p < 0.01$). TDSV did not change from the supine to the head-down tilt position: 113 ± 12 (mean and SD) (range: 81–137) ml vs. 114 ± 13 (range: 94–133) ml (n.s.). Noninvasive SV tended to underestimate TDSV in HDT20; the offset was −4_7 ml (n.s.) for $MFSV_{FINAP}$ and −6_6 ml for $MFSV_{IAP}$ ($p < 0.05$). From the supine position to HUT30, TDSV decreased 24% to 86 ± 12 (range: 60–103) ml. MFSV overestimated TDSV in the upright body position. The difference from TDSV did not differ for $MFSV_{FINAP}$ (5 ± 2 ml) vs. $MFSV_{IAP}$ (6_3 n.s.). In HUT70, TDSV dropped 51% to 55 (range: 33–83) ml; the offset of $MFSV_{FINAP}$ from TDSV was 3_8 ml (n.s.) and 11_10 ml ($p < 0.01$) for $MFSV_{IAP}$. There was no systematic trend in the difference between FINAP and IAP during head-up tilt. From horizontal to STD, TDSV decreased 40% to 68 (range: 41–94) ml. The offset induced by STD was smaller for $MFSV_{FINAP}$ (3_9 ml; n.s.) vs. $MFSV_{IAP}$ (12_9 ml; $p<0.01$). In all but one subjects $MFSV_{finap}$ tracked TDSV in all body positions even during prolonged 70_ passive head-up tilt up to one hour.

In young adults TDSV for all tested body positions is indicated by MFSV with limited offsets over the full range of stroke volume changes observed. FINAP yields smaller offsets than IAP. Offsets may be due to changes in aortic transmural pressure subsequent to orthostasis not accounted for by the model.

Reference ranges for clinical autonomic function testing in the elderly

N.R. Stout, R.A. Kenny

Cardiovascular Investigation Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Introduction: The clinical assessment of the autonomic nervous system is important in the investigation of suspected autonomic dysfunction. A battery of clinical tests are routinely used to determine sympathetic and parasympathetic function (Ewing & Clarke, BMJ 285:916–918). The application of these tests in the elderly is limited, and there are no accepted reference ranges.

Aims: To determine reference ranges for a battery of autonomic function tests in healthy elderly.

Methods: Subjects were recruited and underwent health screening. A battery of autonomic function tests were then performed, using a paper ECG trace and Finapres(c) phasic BP measurement. The test battery consisted of,

—Lying to standing maximum/minimum 30:15 ratio
—Maximum Valsalva ratio and systolic BP response to phase 4 of three successive Valsalva manouvres
—Heart rate response to 6 cycles of rhythmic deep breathing
—Diastolic BP response to a cold stimulus

Results: Fifty four volunteers were recruited with an average age of 68 years (range 60–93 years). There were 34 males. The arithmetic means, SD and lower 2.3 centiles for each test are given in Table 1.

Table 1. Results of autonomic function tests

Test	Arithmetic mean	SD	Lower 2.3 centile
Max/min 30:15 ratio	1.23	0.13	1.06
Valsalva ratio	1.41	0.49	1.12
Heart rate response to deep breathing (beats per minute)	6.4	2.4	1
Systolic BP overshoot to Valsalva (mmHg)	20	2.8	5
Diastolic BP response to cold stimulus (mmHg)	12	1.8	4

Conclusions: The autonomic function test battery used provides is a useful clinical tool in the assessment of autonomic function in the elderly. We have established working reference ranges for a group of healthy elderly subjects for use in our centre. Healthy elderly show a decline in autonomic function, but autonomic dysfunction is not a feature of normal ageing.

Real-time sequence of autonomic responses in anoxic seizure

P.O.O. Julu, S. Hansen, F. Apartopoulos, G.A. Jamal

Peripheral Nerve and Autonomic Unit, Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland

Anoxic seizure or "severe breath holding episode" in children is associated with extreme bradycardia often leading to asystole. It is speculated that the bradycardia or asystole is due to excessive increase in cardiac vagal tone (CVT) caused by defective autonomic reflexes. The current hypothesis is that cerebral anoxia resulting from the bradycardia or asystole would lead to a seizure, in which case, atropinization to prevent the rise in CVT would be a rational means to prevent such seizures. We have monitored multiple autonomic indices in real-time during anoxic seizures in a 2 year old known sufferer of the disease.

EEG was measured using electrodes arranged in a head cap according to international 10:20 reference system. Heart rate (HR) was obtained from the ECG R-R intervals. Breathing movements were measured using resistance plethysmography. Arterial mean, systolic and diastolic blood pressures (BPs) were measured non-invasively using the Finapres. Changes in CVT were monitored continuously by phase demodulation of heart periods using the NeuroScope as has been previously described. Transcutaneous pO_2 and pCO_2 were measured continuously using oxygen and carbon dioxide sensitive membranes in the Radiometer.

An attack was precipitated by attempt to adjust the breathing plethysmograph. It started with a short cry, followed by successive cough-like chest movements that ended with apneusis. Opisthotonus followed and a very brief period of hypotonia, then muscle twitches and a subsequent recovery allowed the child to continue crying. Generalised, monotonic, and large EEG delta waves preceded all events and this started concurrently with a selectively sympathetic excitation indicated by ramp increases in HR and BPs. There was no significant change in CVT from the baseline level for 65 s following the start of EEG abnormality, then a sharp and sudden increase in CVT caused a marked bradycardia, but there was no asystole. The sudden increase in CVT coincided with a type of breathing where successive expirations were larger than inspirations. A steep fall in transcutaneous pO_2 and a gradual rise in pCO_2 started 27 s after the apneusis and were ended by crying at the end of the seizure.

These results suggest that cortical events can precede those in the brainstem by at least one minute causing sympatho-vagal imbalance in anoxic seizures. In this case, anoxia was due to apneusis

and not the bradycardia caused by the brief but large increase in CVT. Therefore, atropinization would not have been effective in preventing the seizure. This patient highlights the drastic and sudden changes in autonomic tones that can occur in certain clinical conditions. Such changes can be detected only by real-time monitoring of multiple autonomic indices for a meaningful interpretation.

Cold intolerance in Fabry patients suggests hypothermia induced small nerve fiber hypoxia

B. Stemper[1], M.J. Hilz[1,2], E.H. Kolodny[2]
[1]Dept. of Neurology, University of Erlangen-Nuernberg, Germany;
[2]Dept. of Neurology, New York University, New York, NY, USA

In Fabry disease, an X-linked a-galactosidase A deficiency, painful crises and limb paresthesias are frequent, poorly understood, and possibly linked to thermal exposure. Function of temperature and pain mediating small nerve fibers has not yet been tested after cold challenge. We hypothesize that there is small fiber dysfunction with cold exposure.

Therefore, we studied thermal perception thresholds before and after cold stimulation in two brothers with Fabry disease (15 and 17 years old), their 19-year-old healthy sister and their 45-year-old mother, a disease carrier, and eight healthy controls (mean age 27.4 ± 10.3 years). In all participants, we assessed cold and warm perception thresholds at the dorsal foot and the lower medial calf before and 1, 5, 10 and 15 min after 30 s cold exposure of one leg, using the method of limits and a Somedic-ThermotestÔ (Stockholm, Sweden). The leg was immersed into 5°C water up to the mid-thigh and discomfort was rated on a 0–10 visual analog scale (VAS).

Before cold stimulation, thermal thresholds of all participants were within normal age related limits. In contrast to controls, the Fabry patients tolerated 30 s cold stimulation only with interruptions after 15 s and 20 s. The mother tolerated cold for 6 s only. The patients and their mother reported intense burning pain and numbness during and after stimulation. After cold exposure, the patients experienced paradoxical thermal sensation, thresholds were highly elevated and normalized after 20 min in one and 80 min in the other brother. The thermal thresholds of the healthy persons were somewhat elevated after stimulation but normalized within 10.0 min ± 4.6 min. Discomfort during cold exposure was rated 8–10 by the patients and their mother, but 3–5 by the healthy persons.

The Fabry patients and their mother showed cold intolerance and small fiber dysfunction with impaired thermal perception and dysesthesia after cold exposure. We speculate that this dysfunction is due to a hypothermia induced hypoxia which might originate from glycolipid accumulation in small nerve vessel walls.

Assessment of baroreflex sensitivity using spectral and cross spectral analysis in syncopal patients

*G. Gulli, V.L. Wight, R. Hainsworth
Institute For Cardiovascular Research, University of Leeds, UK
*Institute of Human Physiology, University of Verona, Verona, Italy

The aim of this study was to examine non-invasively whether baroreceptor dysfunction may contribute to poor blood pressure control in syncopal patients.

Twenty patients with histories of unexplained syncope underwent a combined head-up tilt (HUT) and lower body suction test. Ten patients developed presyncope at a stage earlier than predicted (fainters) and 10 had normal tolerance[1]. We recorded R-R period (ms) and blood pressure (mmHg) continuously from the ECG and Finapres. Autoregressive monovariate and bivariate models were fitted to each time series. The powers and central frequencies associated with each spectral peak were automatically quantified and transfer function gain in the low frequency (LF) was taken as an estimate of baroreflex sensitivity (BRS). Values are reported as means ± SE.

No differences were observed between the two groups in time or frequency domain of any variables during supine. Tilt resulted in similar responses of RR period in both groups but the change in systolic pressure was different. In fainters it changed non-significantly from 127.8 ± 7.3 to 117.5 ± 3.4 whereas in non-fainters it increased from 117.5 ± 3.8 to 124.1 ± 4.9 ($P < 0.05$). Tilt produced a significant increase in LF power of systolic pressure in both groups but an abnormal decrease in LF power of RR in fainters. Fainters also exhibited a significantly greater decrease in BRS as measured by transfer function gain (67.6% versus 31.5%, $P < 0.05$).

The LF oscillations of RR period are thought to be vagally mediated through the baroreflex and are secondary to sympathetically induced changes in blood pressure[2]. The decreases in LF oscillations of RR period which occur in fainters despite normal blood pressure oscillations can be explained by the abnormally large decrease in BRS which was also shown by transfer function gain.

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Pupillary response during Ewing maneuver demonstrates central sympathetic overreactivity in familial dysautonomia

M. Dütsch[1,3], M.J. Hilz[1,3], U. Rauhut[1,3], J.M. Solomon[2], E.H. Kolodny[1], B. Neundörfer[3], F.B. Axelrod[1]
Depts. of Neurology[1] & Ophthalmology[2], NYU, New York, NY, USA;
Dept. of Neurology, University of Erlangen-Nuremberg, Germany[3]

In Familial Dysautonomia (FD), central autonomic function is still poorly understood. Previous studies suggest a mismatch between peripheral sympathetic failure and preserved or excessive central sympathetic regulation (1).

To further pursue this hypothesis, we compared the—more centrally mediated—pupillary response to peripheral cardiovascular responses during Ewing maneuver.

In 10 FD-patients (6 female, 4 male, mean age 21.6 years) and 8 healthy controls (6 female, 2 male, mean age 24.5 years), pupillary diameter and tonometric systolic and diastolic radial artery blood pressure (BPsys, BPdia) (Colin Pilot, San Antonio, TX) were measured at rest, in sitting position, and after one minute active standing. In addition, the 30:15 heart rate ratio was calculated. Resting and standing pupillary diameters were averaged over a 4 seconds period using a CIP9.08-pupillograph (AMTech, Weinheim, Germany). In all patients, an ophthalmologist had ruled out refractory media pathology.

In patients, pupillary diameter increased by 10.6% from 5.4 mm at rest to 5.9 mm during standing. In controls, there was only a 1.3% increase from 6.3 mm at rest to 6.4 mm standing (Mann-Whitney-U-test: $p < 0.01$). The 30:15 ratio was significantly lower in patients (1.11 ± 0.06) than in controls (1.30 ± 0.13; $p < 0.01$). In patients, BPsys had dropped by 25.4 mmHg and BPdia by 22.7 mmHg after one minute standing. In controls, there was no significant BP decrease (BPsys: −1.0 mmHg; BPdia: −0.6 mmHg) (U-test: BPpatients vs. BPcontrols: $p < 0.01$).

The results confirm a discrepancy between peripheral cardiovascular sympathetic failure and sympathetic overreactivity of the—more centrally mediated—pupillary response during active stand-

ing. The findings further support the hypothesis of increased central sympathetic activation during peripheral sympathetic failure in FD[1].

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Decrease in cardiac variability with increase in vagal tone

V. Bothams, M. Farmer, J. Fletcher, S. Maung, J.H. Coote, J.N. Townend

Department of Physiology, The Medical School, The University of Birmingham, Birmingham, UK

The heart rate of resting healthy subjects normally shows a respiratory related arrhythmia (RSA) in which it increases during inspiration and decreases during expiration. The variation in beat to beat interval (R-R variability) during each respiratory cycle is considered to be dependent on changes in cardiac parasympathetic (vagal) activity since it is absent after peripheral cholinergic blockade with atropine. Therefore R-R variability is considered as an index of cardiac vagal tone. We report here examples in which this positive relationship of RSA and degree of vagal tone is apparently reversed. Subjects were tested in a semi supine position and ECG and respiratory movements (rate and depth) recorded. The magnitude of RSA was measured using both time and frequency domain analysis at fixed respiratory frequency and tidal volume. Of five subjects (20–22 years) examined so far two non athletes who had not undertaken regular sporting activity had resting heart rates of <50 bpm and showed a low RSA compared to a control group and a smaller high frequency (HF) peak in the power spectral analysis. Another two subjects undertook endurance training (8 weeks) which improved their VO2 max by 10% and decreased their heart rate from >50 bpm to <50 bpm. The magnitude of RSA and the HF peak decreased in these two subjects compared to their pre-training values. Studies on one 'elite' endurance athlete who had a low resting heart rate (<50 bpm) showed a small RSA and HF peak but of interest was the finding that RSA and the HF peak could be increased by mild exercise related stimuli. At present we interpret these findings as suggesting that central interaction between respiratory influences and cardiac vagal neurones becomes less effective at very high levels of cardiac vagal tone.

The possible role of prolactin assay in the differential diagnosis of Parkinson's disease and multiple system atrophy

A.S. Winkler*, K. Ray Chaudhuri

Movement Disorders Unit, King's College Hospital, London, UK

The hypothalamic-pituitary axis may be involved early in multiple system atrophy (MSA). However such involvement in idiopathic Parkinson's disease (IPD) is not clearly documented. Prolactin is involved in the hypothalamic-pituitary axis and levels increase with orthostatic stress.

In a preliminary study to assess whether prolactin levels could distinguish between MSA and IPD patients, we studied 6 patients with MSA on levodopa treatment (mean age 62.5 ± 3.5 years, mean duration of disease 7.5 ± 4 years), 6 MSA patients on no levodopa treatment (mean age 63.8 ± 9.5 years, mean duration of disease 5.5 ± 4 years), 10 IPD patients on dopaminergic treatment (mean age 62.8 ± 10.5 years, mean duration of disease 4.1 ± 2.2 years) and 5 drug naive IPD patients (mean age 63.8 ± 9.8 years, mean duration of disease 5.9 ± 5.4 years). Three normal individuals were studied (mean age 40.6 ± 10.3 years). Prolactin levels were measured in the supine position after 15 minutes rest and during 60° head-up tilt, blood being taken at 5 and 15 minutes during tilting.

There were no significant differences in baseline prolactin values between both groups of MSA and IPD patients and controls. There was a trend in MSA patients to have high prolactin levels (356 ± 109 mu/l) in comparison to controls (140 ± 64.4 mu/l). Orthostatic stress did not alter prolactin levels significantly. There was a moderate increase in prolactin levels in normal individuals during head up tilting.

We conclude that prolactin levels may not differentiate between MSA and IPD. Furthermore, orthostatic stress appears to have minimal effect on prolactin levels in MSA and IPD.

Autonomic change in mitral stenosis

M.J. Bettencourt, B. Gomes Pinto, E. Infante de Oliveira, L. Silva-Carvalho, J. Silva-Carvalho

Lab Moniz de Bettencourt do Instituto de Fisiologia da Faculdade de Medicina e Hospitais Civis, Lisbon, Portugal

Examining cardiovascular response to orthostatism, we previously observed changes in autonomic nervous system function in essential hypertension[1,2], in not vertiginous complete left bundle block and in not vertiginous chronic atrial fibrillation (CAF)[3,4]. This last autonomic dysfunction suggests the presence of an anomalous left atrial reflex. With the aim to improve our knowledge about A-type and B-type atrial receptors reflexes we presently studied mitral stenosis in sinus rhythm and compared results with those from CAF and healthy subjects (N).

We examined 20 N, mean aged 53 ± 12 years, 20 CAF, mean aged 59 ± 13 years, 16 mitral stenosis with a mildly dilated left atrium (LA = 24.2 ± 2.9 mm/m^2) (MS1), mean aged 47 ± 11 years, and 14 mitral stenosis with a moderately dilated left atrium (LA = 27.7 ± 2.9 mm/m^2) and mitral regurgitation (MS2), mean aged 55 ± 10 years. Atrium dimensions were significantly different ($p < 0.01$). In both groups mitral valve area were not significantly different (MVA = 1.7 ± 0.3 cm^2). They were observed in clinostatism, after 15 min rest (CLINO), and after 1 min of orthostatism (ORTHO). Using electrical thoracic bioimpedance BOMED) NCCOM3 assembly and measuring systemic blood pressure by sphygmomanometry, we could determine stroke volume (SV), inotropic index (INOI), total vascular resistance (TVR), cardiac work (W), aortic compliance (AC), stroke work (SW), heart rate (HR) and thoracic fluid index (TFI). We analysed means of 60 heart beats. MS1 and MS2 TFI were significantly different ($p < 0.05$). For MS2, TFI was low, denoting an augmented pulmonary blood volume.

For MS1 and MS2 cardiovascular variables values in ORTHO and CLINO were linearly related. Except for HR, MS1 had significantly the same linear correlations as N and MS2 had significantly the same linear correlations as CAF, presenting an increase in SV (fig. 1), INOI, W, AC and SW and a decrease in TVR in orthostatism. Percentual value of INOI in ORTHO relative to CLINO vs percentual value of SW correlation was also for MS1 identical to N and for MS2 identical to CAF. For HR, we found linear correlations identical to N, for all patients groups.

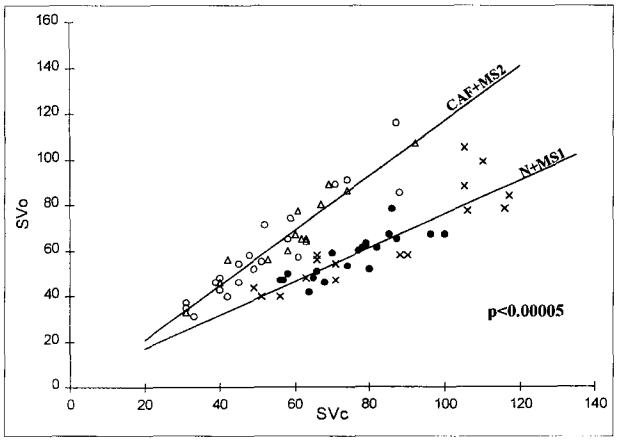

Figure 1. SV linear regressions.

Results show an autonomic change for dilated atrium mitral stenosis in agreement with an atrial B-type receptor reflex[5]. The fact that this reflex is observable only when left atrium is dilated can signify that it takes place over a certain threshold of atrial tension.

As correlations for dilated atrium mitral stenosis and for atrial fibrillation, which does not present atrial contraction, are significantly the same, a cardiovascular variables change due to A-type receptors can be compensated by other cardiovascular receptors. It is also possible that atrial contraction is diminished due to atrial dilatation or mitral regurgitation, and alternatively that A-type atrial receptors does not really respond to atrial contraction. In the second case this would mean that A-type receptors have a pressure threshold.

The observed occurrence of linear relationships between cardiovascular variables values in ORTHO and CLINO in healthy subjects and also in some pathologies, being different from normal and distinct for different autonomic dysfunctions, signifies that there are favoured states in blood circulation controlled by autonomic nervous system. During postural change, in pathologies in which an anomalous reflex or the impairment of a reflex take place, a new well characterised favoured equilibrium between reflexes and hemodynamic effects is established. Cardiovascular variables values change from one favoured state to another is perfectly ruled, conducing to a collective behaviour also ruled.

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Chronic fatigue syndrome or sympathetic neuropathy

A. Riedel*, S. Braune*, R. Macharzina†, CH Lücking*

*Department of Neurology, University of Freiburg, Germany

†Department of Internal Medicine, University of Freiburg, Germany

A 59-year-old female patient fell ill with symptoms of an infectious disease in March 1998 from complete healthiness. She reported fever, red tonsils, tender lymph nodes, muscle-ache, sporadic episodes of diarrhoea and a loss of appetite. Two weeks later she developed orthostatic dizziness and daily episodes of syncope. She could not walk more than 10 meters because of blurred vision. In two months the patient lost 20 kg of weight. On direct questioning she described a burning pain in her toes. Initially infection parameters were slightly elevated (Leukocytes 11.3, CRP 0.55 mg/dl). In May no abnormalities could be found in plasma apart from an elevated ferritin (790 mg/ml). CSF did not show abnormalities. No neoplasm was found in an extensive tumour search. Circadian cortisol rhythm was preserved. Nerve conduction studies were slightly slowed with conduction velocity of 38 m/sec for the peroneal nerve and 33 m/sec for the sural nerve.

Initially a Chronic Fatigue Syndrome was diagnosed.

In May 1998 active orthostatis had to be interrupted because of presyncope after 30 seconds in upright position. Blood pressure fell from 100/56 mm Hg to 56/40 mm Hg while heart rate rose from 105 bpm to 12 bpm. Blood pressure regulation in Valsalva-manouevre showed a fall of blood pressure in phase Ile and a lack of overshoot in phase IV. The latency III-IV was 11.6 seconds while the Valsalva ratio was 1.2. The sympathetic activation of heart rate in orthostatis was preserved. In a QSART, which was performed at the forearms, the lower legs and the toes, no sudomotor response was obtainable. Normal norepinephrine levels on plasma were found supine and upright. No involvement of vagal function could be demonstrated by heart rate variability during deep breathing. No complaints of dry mouth or dry eyes were indicated by the patient. Bladder function was normal.

Sleeping 15° head up tilted and with the medication of 40 mg/d midodrine, 5 mg/d bisoprolole and 0.2 mg/d fludrocortisone the patient became mobile again and could walk 100 m without symptoms of orthostatic hypotension.

Severe acute postviral autonomic neuropathy, which specifically affected the distal sympathetic neurons (cholinergic sudomotor and adrenergic vasoconstrictors) was diagnosed. Accurate autonomic function tests are necessary to differentiate postganglionic affection of the autonomic nervous system from Chronic Fatigue Syndrome.

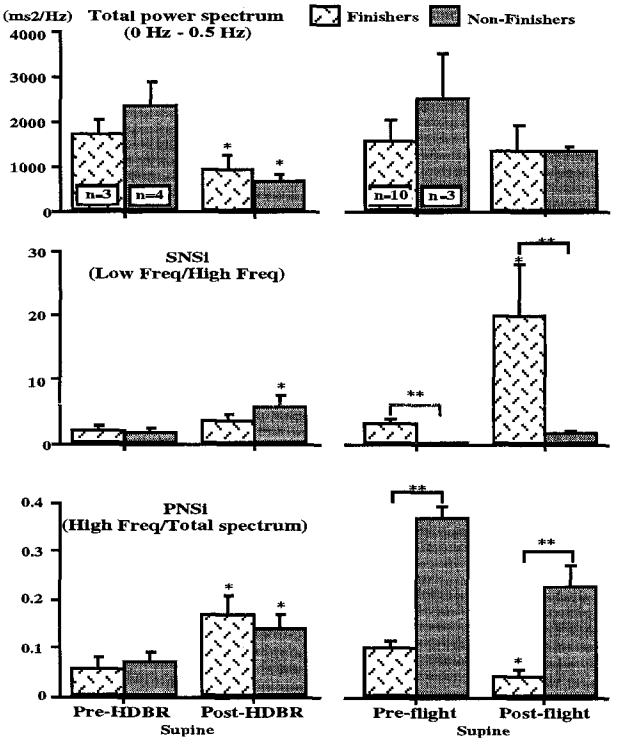
Sympatho-vagal changes and orthostatic intolerance after simulated or actual microgravity

D. Sigaudo-Roussel, R. Karpranski, C. Gharib, J.-O. Fortrat

Laboratoire de Physiologie de l'Environnement, Faculté de Médecine Lyon Grange-Blanche, 8 avenue Rockefeller, F-69373 Lyon Cedex 08, France. Star City, Moscow region, Russia.

Possible changes in autonomic nervous regulation could be linked to orthostatic intolerance (OI) that occurred on subjects after a long-term spaceflight or head-down bed-rest (HDBR). To assess this hypothesis, we studied the sympathetic nervous system during simulated or actual microgravity using spectral analysis of heart rate variability (1).

It seems that subjects who exhibited an OI had a greater sympathetic influence (SNSi) than those who finished the stand test after a long-term HDBR which could participate to OI (2). We studied cardiovascular responses in supine position before and after spaceflights lasting up to 6 months. We observed a subnormal SNSi in the non-finishers subjects in supine position which could result in an OI. However, the increase in SNSi in the finishers subjects was mainly due to a withdrawal of the parasympathetic influence (PNSi).



* $p < 0.05$, ** $p < 0.01$ vs pre-measurement.

Fritsch-Yelle et al. (3) reported a subnormal norepinephrine level in standing presyncopal astronauts but did not observe any differences in supine position on landing day. In fact our study suggested different regulating mechanisms of the sympatho-vagal balance between finishers and non-finishers subjects and between simulated and actual microgravity. These differences between subjects and between post-HDBR and post-flight results could be linked to the different environmental conditions.

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Electroautonomography: a non-invasive apparatus to assess autonomic nervous system function

E.N. Lerner
Lerner Medical Technology B.V., Amsterdam, The Netherlands

Electroautonomography (EAG) is suggested as a method of diagnosing disorders of the autonomous nervous system (ANS). The essence of EAG is the recording of the electrical skin responses on the palms of the hands and the soles of the feet[1]. The graphs are then analyzed and interpreted. An EAG has been developed by Dr. Lerner (patent N 1362445, 1987)[2]. An eight channel easy manageable EAG device has recently been developed.

The EAG apparatus consists of a stimulator and a monitor that can be connected to a personal computer. The stimulator can give an electrical stimulus, a sonic stimulus or both. In our studies, we give the following stimuli to subjects: sound, electricity, mental arithmetic, deep breathing and the Valsalva.

The monitor holds eight channels. Four of the channels are used for EAG; one for ECG and one for electrogastrography (EGG). The two remaining channels can be used for respiration, pH, blood pressure and others.

Methods: Ag/AgCl electrodes are fixed to the palms and on the soles. Reference electrodes are fixed to the back of the hands and the feet to measure the electroautonomogram. Measurements on 400 patients has revealed the following distribution of EAG signals in this population:

Signal type:	I	II	III	IV	V
Percentage:	6%	31.5%	39.6%	18.8%	4%

I	Hypersympathicoactivity
II	Presympathicoactivity
III	Normoactivity
IV	Preparasympathicoactivity
V	Hyperparasympathicoactivity

The signals have been classified by comparing the EAG signals to classic clinical evaluation of the autonomous nerve system using different techniques, such as heart-rate, blood-pressure, respiration, dermographism, limb sweating, Ashner's test and others.

There is a 95% correlation between the classical clinical evaluation and the EAG signals.

After administration of epinephrine, the EAG signal flattens whilst blood pressure and heart rate rise. Also, after administration of nicotinic acid, the EAG signal rises whereas blood pressure and heart rate decrease. The EAG apparatus can determine lesions in the central part of the ANS, it can also show autonomic hemisyndrome as a result of lesions in a hemisphere of the brain, as well as damage in the proximal or distal parts of the peripheral autonomic fibers in the extremities which indicates a polyneuropathy. The EAG apparatus can determine the autonomic control of heart-rate, respiration and gastro-intestinal functions.

The EAG apparatus also shows predominance of sympathetic and parasympathetic activities.

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