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4th EUROPEAN FEDERATION OF AUTONOMIC SOCIETIES (EFAS) MEETING

May 16-18, 2002, Astir Palace Resort, Vouliagmeni, ATHENS-G R E E C E

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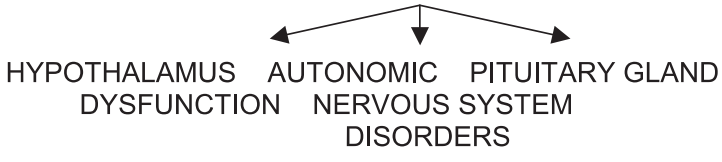

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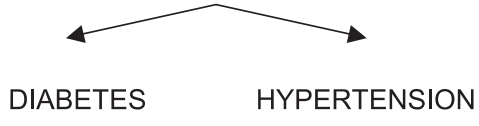

Abstracts of the Invited Speakers

Structure and chemical composition of the autonomic nervous system on the spinal cord

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The nervous tissue is structurally specialized to be exited selectively by various stimuli and to contact nervous impulses rapidly to the glandular epithelial cells and the muscle cells. The efferent neurons concerned in the innervation of the smooth and cardiac muscles and the glands of the body constitute the autonomic nervous system. The function of the autonomic nervous system is to regulate the activities of many visceral structures and organs that possess a high degree of independence. The sympathetic and parasympathetic divisions of the autonomic nervous system are functionally antagonistic to each other in maintaing a balance in the tonic activities of the visceral organs. Both sympathetic and parasympathetic divisions arise in the CNS but from different parts of it. Two efferent neurons (preganglionic and postganglionic) are required to join the CNS with the peripheral sites of innervation.

The autonomic ganglia are composed of ganglion nerve cells separated by a connective tissue framework. They are multipolar, in contrast to the cerebrospinal ganglia cells, which are unipolar; in addition they are smaller mostly with eccentrically located nuclei. The terminal parasympathetic ganglia may be very small, even consisting of a single ganglion cell.

During the development of the peripheral nervous system, cells migrate from the neural crest to form the ganglia of the sympathetic and parasympathetic autonomic division. Neurons migrate to specific locations according to biochemical interactions with the local environment, other neurons, and glia.

In the sympathetic division, the preganglionic neurons originate in the gray matter of the anterior and posterior column of the spinal cord, located in the thoracic and upper lumbar portion. The nerve cell bodies are small with few Nissl bodies and they give rise to lightly myelinated axons; when grouped, they form the white communicating rami. These preganglionic fibers synapse in the cell bodies of postganglionic neurons, which are collected into two chains of paravertebral ganglia, one on each side of the vertebral column, and into several prevertebral ganglia. Axons of the sympathetic ganglion cells are thin but are unmyelinated. Most postganglionic fibers pass via gray communicating rami to spinal nerves. The postganglionic fibers of the prevertebral ganglia form the hypogastric, splachnic and mesenteric plexuses.

The parasympathetic division comprises two separate parts of the CNS: the cranial and the sacral part. The preganglionic fibers of the cranial part are situated in nuclei of the gray matter in the medulla and the midbrain; these fibers make their way out of the CNS by way of the 3rd, 7th, 9th and 10th cranial nerves. The sacral part of the parasympathetic division originates in the lateral horn cells of the 2nd, 3rd and 4th sacral segments. Axons of these neurons, representing the preganglionic fibers, traverse the sacral nerves and synapse in ganglia located within the walls of the distal colon, bladder, and other pelvic organs. The preganglionic fibers of the parasympathetic division are usually longer that those in the sympathetic division. The postganglionic fibers represent the axons of cell bodies, which are situated in the ganglia and terminate in the nerve endings in glands and muscles.

The terminals of autonomic nerves and their junctions with smooth muscle and glands are difficult to visualize. As the postganglionic axons enter an organ, usually via the vasculature, they ramified into many small branches and pass without Schwann cell covering among the smooth muscle fibers and the glands. At the ends of the postganglionic fibers and in part along their course there are swellings. The axonal swellings display synaptic vesicles; some of them are clear containing acetylcholine, whereas others containing catecholamine, particularly norepinephrine have a densely granular core.

The autonomic neuroefector junction between autonomic nerve fibers and smooth muscles is rather a muscle bundle representing sites of electronic coupling. By electron microscopy, these sites are identified as gap junctions; their size varies from punctuate junctions to junctional areas of more than 1 μm in diameter. In addition, the autonomic neuromuscular junction is not a synapse with a well-defined structure. Unmyelinated postganglionic nerve fibers reaching the effector smooth muscle become beaded or varicose. These varicosities are not static; they are 0.5–2 μm in diameter and are packed with vesicles and mitochondria. Neurotransmitters from autonomic nerve fibers are released from these varicosities at intervals of 5–10 μm along axons. Neurotransmitter is released *en passage* from varicosities during conduction of an impulse along an autonomic axon. Release of a neurotransmitter produces a transient change in membrane potential of the postjunctional cell. If a single pulse results in depolarization, the response is called excitatory junction potential; if the result is hyperpolarization, the response is called inhibitory junction potential.

The classic aspect of autonomic nervous control as antagonistic actions of noradenalin and acetylcholine, resulting in constriction and relaxation respectively, was modified when clear evidence of a non-adrenergic, non-cholinergic (NANC) system was presented. ATP was the first substance that was found to fulfill the criteria for a neurotransmitter in nerves of this system. Subsequently, several bioactive neuropeptides and transmitter synthesizing enzymes in neural elements, identified by immunohistochemistry in the mammalian autonomic nervous system have now been proposed as neurotransmitters. Various different biological amines such as serotonin and dopamine are known to be autonomic neurotransmitters. Neuropeptides are synthesized in the nerve cell body and transported along the nerve fiber to the sites of release. In contrast, repute and synthesis of other neurotransmitters occurs at the axon terminal. Lastly, several hormone and growth factor receptors have been identified in the autonomic nervous system, although their characterization, significance and sites of expression in most of them remain to be elucidated.

Evidence of autonomic dysfunction in the etiology of functional urethral obstruction

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Functional urethral obstruction (FUO) is characterized by urethral narrowing only during voiding. The diagnosis of functional urethral obstruction relies on previous exclusion of causes of organic, i. e. permanent stenosis.

Differential diagnosis of FUO includes bladder neck (BN) obstruction, various causes of "organic" urethral obstruction (valves, etc.), detrusor external sphincter dyssynergia (DESD), and detrusor internal sphincter dyssynergia (DISD).

The characteristics of BN obstruction are the following:

1. Increased intravesical pressure before BN that drops immediately after BN level [requires an urodynamic (UD) study]
2. Indirect evidence from bladder trabeculation, diverticula, and increased postvoid residual.
3. Diminished maximum and average urinary flows

During the process of normal voiding, just before the onset of bladder contraction there is a drop of the intraurethral (intraluminal) pressure which is recorded at the level of the external urethral sphincter (EUS), followed by an increase in the intravesical pressure which is the detrusor contraction. During detrusor contraction there is an electrical silence (recorded by EMG) reflected as continuing relaxation of the EUS during the entire voiding phase.

On the contrary in DESD the intraurethral pressure rises before

the onset of bladder contraction to levels higher than the resting phase (level of the EUS). Depending on the type of DESD we have to note the following:

In DESD type I, during bladder contraction the intraurethral pressure is increased until the bladder contraction reaches its maximum magnitude, and then there is an immediate drop of the intraurethral pressure. Because of the highly increased intravesical pressure prior to the urethral opening the above sequence of events results in super normal flow. The EMG recording from the EUS shows increased activity which ceases when the bladder contraction reaches its maximum.

In type II DESD there is intermittent contraction of the EUS during bladder contraction and characteristically there are peaks of EMG activity that even though they do not result in detrusor contraction inhibition, they are causing intermittent bursts of urinary flow synchronous with the interposed sphincter relaxation phases.

Type III DESD is a more severe voiding disorder, characterized by continuous non relaxation of EUS. This results in inability to void and is obvious that is related to increased morbidity. I would consider treating this disorder as of urgent priority.

In 1983 (Barbalias et al., J Urol, 130:514–517) we described patients who had been studied urodynamically with synchronous video pressure-flow studies with EMG of the EUS with the clinical syndrome of prostatodynia.

The most striking finding was a significant increase in maximum urethral closure pressure (MUCP) and typically peak and average urinary flow rates were decreased. Another prominent feature was incomplete funneling of the BN during voiding with an accompanying urethral narrowing at the level of the EUS.

These findings were not consistent with a diagnosis of tension myalgia of the pelvic floor, or detrusor striated sphincter dyssynergia, but suggested a primary abnormality involving the pelvic sympathetic nervous system. This hypothesis was further confirmed by alpha blockade which resulted in decrease of MUCP, normalization of the video-urodynamic findings, and a dramatic improvement both in symptomatology and urinary flow rates. Furthermore, upon the discontinuation of alpha blockers the patients reversed to prior complaints and diminished urinary flow rates (UFRs). On the basis of this data diagnosis of functional urethral obstruction was apparent.

Despite various recommendations and clinical guidelines for prostatitis, it is universally accepted that treating chronic prostatitis syndromes is very difficult in terms of sterilizing a previously positive EPS culture and providing a substantial recurrence free interval. One of the prostatitis literature titans, E. Meares, suggested that cure rate of definitively diagnosed bacterial prostatitis remains in the range of 50 %.

This observation underlines the difficulties associated with treating bacterial or nonbacterial prostatitis and securing a low recurrence rate. In previous publications we have proposed a link that may "pave the way" to consider a more "dynamic" dysfunction as the primary mechanism responsible for the etiology, the frequent recurrences and the difficulty to nullify positivity of segmental cultures.

What we find in the bacteriological spectrum in the segmental cultures may be a secondary event. Common bacteria found, mycoplasma, Ureaplasma and Chlamydia or cryptic "non culturable" microorganisms cannot necessarily be considered responsible for the "prostatitides".

Convincing but indirect evidence of the above is the unpredictability of clinical response with antibiotics which in turn is not always and thus predictably related to the conversion of a prior positive to a sterile culture. We definitely need to decide "what is cure", i. e. the length of time free of symptoms alone or combined with sterile cultures? Why the antibiotics do not provide cure as should be reasonably expected?

We know a lot more now about pharmacokinetics, the appropriate characteristics of a drug to penetrate into the lumen of the prostatic acini and secure a bactericidal concentration. Exactly for this reason we should ask ourselves why the drugs alone do not work? Why there is no correlation between the elimination of a uropathogenic organism from the EPS and the long term cure of chronic prostatitis?

I would like to draw attention again to a "missing link" in current methodology. Why do patients with negative cultures respond to antibiotics? Is there a placebo effect? Is this fraction of patients statistically significant compared to the group of patients that do not respond to antibiotics?

There is no doubt that in prostatitis syndromes there is a "urinary dysfunction". It is obvious that this dysfunction cannot be explained by just finding E. Coli or Pseudomonas positive cultures, or even more by negative cultures. Apparently we should search for other etiologic factor(s) that are causing this dysfunction, i. e. the missing link.

In several papers we have shown the urodynamic pattern characteristic of prostatodynia or as a better term painful male urethral syndrome (PMUS). In chronic prostatitis the prostate is not in pain as the term prostatodynia implies but *the hallmark of this clinical syndrome is the measured urethral hypertonia. Urethral sensitivity reflects exactly this hypertonia as well as the radiation of pain (or discomfort).*

It is time to move from the bacteriological approach only to a "more dynamic concept" for this syndrome. In previous reports we have described the clinical and urodynamic spectrum of findings characteristic of prostatodynia. However, when we studied patients with same clinical complaints and similar age, but with inflammatory EPS we found no stat. Sign. Differences between the 2 groups of patients as to the urodynamic pattern of the syndrome.

Maximum and minimum urinary flow rate were decreased in the majority but not in all patients. *The high MUCP was attributed to increased adrenergic stimulation caused by local or distant factors allowing reflux of urethral contents primarily into the peripheral zone of the prostate and hence chronic nonspecific prostatitis.*

We have proposed replacing the term prostatodynia with the better term PMUS. In most cases of PMUS there has been a therapeutic clinical response to a- blocking agents with normalization of other urodynamic abnormalities. Failure to respond was associated with either extensive inflammatory changes of the prostate or coinciding benign prostatic hyperplasia.

Residual urine was not found to be statistically different in the PMUS or the abacterial prostatitis group and if recorded was rather related to the painful micturition. In view of the above I believe that chronic prostatitis is primarily caused by intraprostatic urethral reflux and urethral hypertonia is the underlined pathophysiological mechanism.

In a recent publication (Barbalias et al., J Urol, 1998;159:883–887) we embarked upon a comparative study by using alpha blockers for the treatment of chronic prostatitis in combination with antibiotics. Three groups of pts were studied including pts with abacterial prostatitis, prostatodynia (PMUS), and chronic bacterial prostatitis.

Alpha blockers were administered in the first 2 groups of pts and to 50 % only of pts with chronic bacterial prostatitis. Antibiotics were given to all patients with positive EPS cultures and in half of those with abacterial prostatitis.

The results of this study has shown that the recurrence rate of bacterial prostatitis was significantly reduced by alpha blockade (EPS culture negative) and symptom relief was achieved for many months. In abacterial prostatitis statistical analysis showed a lower symptom recurrence rate in pts receiving only alpha blockers in comparison with those treated with antibiotics.

As a final conclusion of this study, using alpha blockade was justified not only for PMUS but also abacterial and bacterial prostatitis in which alpha blockade not only caused higher clinical improvement, but also reduced the recurrences as defined by EPS positive segmental cultures.

It is obvious that the results of our last study are confirmatory and further strengthen our initial suggestions regarding the pathophysiological mechanism which is operative in the etiology of this dysfunction.

Diagnostic procedures in patients with neurologic dysfunction of lower urinary tract

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Conceptually, assessment of the patient with lower urinary tract (LUT) dysfunction consists of the evaluation of LUT function, the evaluation of LUT neural control, and the ascertainment of etiological diagnosis of the LUT disorder. Thus, syndromic diagnosis of LUT dysfunction, definition of the neural control impairment, and the diagnosis of the responsible disease should ideally be obtained. The procedures necessary for reaching this comprehensive diagnosis can be listed as those assessing LUT function (including urodynamics), those assessing the impairment of neurocontrol (including clinical neurophysiological tests), and those necessary to reach etiological diagnosis. Accurate functional and pathophysiological diagnosis should allow appropriate management, contributing significantly to the patient's quality of life. In addition to the above concerns – and indeed of primary importance for overall patient's health – is the prevention of upper urinary tract deterioration due to LUT dysfunction.

In practice, the necessity to assess LUT dysfunction occurs in different populations of patients. There are neurological patients with known LUT dysfunction (which may or may not be neurogenic), and patients without known neurological disease who have LUT dysfunction suspected to be neurogenic.

Assessment of LUT function in the neurological patient

In neurological patients with diseases known to cause LUT dysfunction and in which this dysfunction has occurred in a fashion highly suggestive of it being neurogenic, the basic investigations and management can and should be carried out by the neurologist (Fowler et al. 2001). While information on somatic "sensory-motor" body functions (such as hand function, locomotion, etc.) obtained by history (symptoms) can be directly clarified by clinical examination (signs) this is not the case with sacral functions. For clarification of urinary symptoms instrumental investigation is necessary.

In neurological patients with urinary symptoms the most important issue is the measurement of the post-void residual (PVR). The extent of incomplete bladder emptying cannot be reliably ascertained from patient history, thus PVR is of primary interest in the patient with neurogenic voiding dysfunction. In addition, in the patient with bladder storage dysfunction, PVR worsens hyperreflexic detrusor contractions. PVR will also lead to urinary infections. PVR can be measured (after a normal void) by an "in-out" catheterisation or ultrasound. Handy ultrasound scanners are available for use in the neurology outpatient clinic or department. It should be kept in mind that the amount of PVR may not reflect detrusor contractility, as the "normal void" can be effected by abdominal straining, bending forward or applying direct pressure to the lower abdominal wall by the patient.

Uroflowmetry measures urinary flow. It is a non-invasive test indicated in the assessment of voiding disorders. The maximum flow rate, mean flow rate and volume voided are assessed in conjunction with the uroflow "curve" (which is bell-shaped for the normal void). Uroflowmetry combined with ultrasound measurment of PVR is a screening test to exclude serious outflow obstruction and can provide information for bladder management in neurological patients (Fowler et al. 2001). It needs to be stressed that it is not possible to distinguish between low flow secondary to detrusor failure and bladder outlet obstruction. Also, to interpret a uroflow trace meaningfully the total voided volume should be greater than 150 ml, which is often a problem in neurological patients with CNS disease.

Cystometry is the recording of the pressure/volume relation of the bladder, but as an investigation it in fact provides data on bladder motor and sensory function. It is an invasive test assessing both bladder storage and voiding. It requires urethral catheterisation (to measure intravesical pressure) and an intrarectal pressure line (to measure intraabdominal pressure) to obtain detrusor pressure (by subtracting intraabdominal pressure from the intravesical pressure). Bladder sensation is assessed by asking the patient – during filling of the bladder – to communicate "the first sensation of filling" and "normal desire to void". The information gathered on bladder storage function is: bladder sensation, capacity, detrusor compliance, detrusor stability and urethral competency. In the voiding phase, the relationship between detrusor pressure and uroflow is recorded.

Leak-point pressures can be determined during a pressure-flow study. Abdominal leak-point pressure is the minimum vesical pressure produced by straining sufficient to cause leakage of urine, and is a measure of sphincter competence. It may be of interest to measure function of the denervated sphincter. The detrusor leak-point pressure is the detrusor pressure at which urine leakage occurs. It is a measure of outflow obstruction, and a prognostic factor for development of upper urinary tract involvement.

Cystometry combined with uroflow reveals – the particularly significant – high pressure/low flow voiding pattern which indicates bladder outlet obstruction. This may be a consequence of impaired neural control (as a rule following a lesion between the pons and the lower sacral spinal segments), causing detrusor sphincter dyssynergia, which may either be due to the striated or smooth muscle (bladder neck) component of the sphincter mechanism.

To reveal functional bladder outflow obstruction in patients with suspected detrusor sphincter dyssynergia cystometry combined with fluoroscopy ("video-urodynamics") is the investigation of choice. It visualizes ureteric reflux and the site of bladder outlet obstruction. Detrusor striated sphincter dyssynergia can also be demonstrated by simultaneous recording of cystometry, EMG (demonstrating persistent or increased sphincter muscle activity) and uroflow.

Urologists recommend urodynamics in neurological patients with urinary symptoms because only such investigation (integrated of course with history, examination, voiding diary, etc.) clarifies the often complex dysfunction, allows for rational treatment, and reveals abnormalities compromising the upper urinary tract. A detailed urodynamic investigation is definitely necessary in patients with traumatic spinal cord injury and dysraphism, because high resting intervesical pressures are often present in these patients, and should be revealed at an early stage.

The need of cystometry in all neurological patients with urinary symptoms has been, however, questioned. Undoubtedly the investigation is indicated if there is uncertainty as to the pathophysiological basis of symptoms. This, however, is unlikely in the typical patient with Multiple sclerosis (MS); these patients are – as a rule – also not prone to develop chronic upper urinary tract problems, although the reason for this is not quite clear. MS patients can be managed – focused on symptoms, and after investigating PVR – by anticholinergics and/or clean intermittent self-catheterisation. Thus it has been claimed that cystometry in these patients is indicated only after first line measures fail to treat the patient's problem (Fowler et al. 2001).

Is LUT dysfunction neurogenic?

The necessity to assess whether LUT dysfunction is neurogenic or not occurs in patients with urinary symptoms in whom a thorough previous investigation has not discovered any "urological/urogynaecological" cause. The possibility of an occult neurological condition is often suspected, i. e. either a systemic disease or an isolated lesion of the relevant neural pathways. In the younger patient MS is often suspected but rarely diagnosed. Of the many possible affections of the older adult it is particularly Multiple system atrophy which causes early sacral dysfunction before other symptoms; it is a rare disease, but should not be missed, as LUT surgery may dramatically worsen the patient's quality of life.

To suspect or rule out neurological disease a focused history will provide most informative data. Clinical examination should carefully exclude a spinal cord lesion, since such a lesion is most likely not yet to be clinically apparent. Thus, particularly important is the examination of lower limbs, and the lower sacral segments.

Most patients from the "suspected neurogenic" group, however,

will have a negative history and a normal neurological exam and thus the question arises whether an occult neurological condition can or should be sought further by investigations, particularly clinical neurophysiological testing.

Expert consensus suggested that clinical neurophysiological testing will only exceptionally add information in a patient with a normal neurological exam. It should be considered in patients with lesions in the peripheral sacral reflex arc. The suggested methods are concentric needle electromyography (EMG), and sacral reflex testing (Vodušek et al. 1999). In suspected demyelinative spinal cord disease, somatosensory evoked potentials (SEP) can be contributory. In MS patients with urinary symptoms it has been shown, however, that tibial nerve SEPs are more sensitive to disclose spinal cord involvement than pudendal SEP (Rodi et al. 1996). Other electrophysiological tests (single fiber EMG, pudendal nerve terminal latency, motor evoked potentials, perineal sympathetic skin response, etc.) have been introduced into the uroneurophysiological diagnostic battery, but are considered investigational. In order to be consistent and reproducible, uroneurophysiologic testing should be standardized (Podnar and Vodušek 2001).

Suspected spinal cord involvement will often lead to MR scanning although an abnormality is rarely found in patients with normal neurological exam and SEP (Fowler et al. 2001).

Pathogenetically, LUT symptoms in a neurological patient may either be due to the underlying disease, or to co-existing "urological" pathology. In neurological diseases known to lead to LUT dysfunction this distinction may be difficult. The clinical impression can be supported by looking for strategically placed structural lesions with neuroimaging, and – in selected patients – by performing neurophysiological tests to define the presence and the extent of a neuromuscular lesion. EMG is particularly helpful in demonstrating abnormalities in striated sphincters in patients with compressive and traumatic lesions of the spinal conus and spinal nerve roots (cauda equina). It is also indicated in the patient with suspected Multiple system atrophy, who may present with voiding difficulty; an abnormal anal sphincter EMG may be the only indicator of the disease (if there is no other cause for the denervation). Due to age, urologic abnormalities may be present in such a patient, and are commonly blamed for the problem; but LUT surgical procedures should be avoided, as they as a rule make the situation worse.

Assessment of LUT neural control should, in principle, be relevant before introducing invasive treatment modalities such as implanted electrostimulation devices, but this has not yet been much investigated. Neurophysiogical recordings have been reported as valuable for optimal placement of stimulating electrodes.

Intraoperative neurophysiological identification of dorsal roots which should be spared in rhizotomy has been reported to decrease postoperative LUT dysfunction in children with cerebral palsy (Huang et al. 1997). Other neurophysiological tests have been introduced to prevent intraoperative damage to LUT neural control in spinal surgery (Vodušek et al. 1993).

Conclusion

Diagnostic procedures in the neurologic patient with urinary symptoms should be focused on symptom management and prevention of chronic disease, and should be co-ordinated by the neurologist. In the patient with LUT dysfunction and normal urological findings, the neurologist is asked to exclude neurological disease. Most important is the co-operation of the urologist and the neurologist in the patient with minor urological pathology, who has or might have a neurological disease.

In the future, more detailed assessment of impairment of LUT neural control may become relevant because of introduction of sophisticated urological treatment modalities such as different electrostimulation protocols.

Intraoperative neural function monitoring may prevent inadvertent postoperative neurogenic LUT dysfunction in selected surgical procedures.

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Treatment of the patient with neurogenic urinary bladder

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The primary goal of the treatment of lower urinary tract dysfunction in patients with neurologic disease is preservation of kidney function. The secondary goal is balanced voiding and trying to achieve continence. The neurologic level of the disability is only moderately correlated with the urodynamic state of the lower urinary tract. A urodynamic study should always be the starting point when urologic management of the patient with neurogenic bladder disease becomes necessary. A well performed urodynamic study is able to characterise the storage (filling phase) and the emptying functions (voiding phase) of the lower urinary tract. Depending on the functional state of the bladder and the sphincteric mechanism, the management of a particular patient with neurogenic bladder disease can be composed of the different building blocks that are described in the next section.

Filling phase

Treatment for the hypersensitive and hyperreflexive detrusor during the filling phase.

Medical treatment

Anticholinergic or antimuscarinic drugs like probanthin, oxybutinin and trospium have all been shown to be effective in controlled studies conducted in patients with neurologic disease. These drugs act by preventing acetylcholine stimulated detrusor contractions. Oxybutinin is also effective when instilled intravesically, thereby preventing common muscarinic side effects like dry mouth or accommodation problems. There are as yet no publications on the effects of the newer drug tolterodine in patients with detrusor hyperreflexia. Selective M3 muscarinic antagonist are currently under investigation. It is expected that side effects that are mediated through other muscarinic receptor subtypes will be absent or less pronounced. The *tricyclic antidepressant* imipramine has been used for many years in patients with symptoms of an overactive bladder. Tricyclic antidepressants

have become less popular because of potential cardiovascular side effects. Controlled studies in patients with neurogenic bladder disease are not available.

Vanilloids like capsaicin and resiniferatoxin are used intravesically. These socalled c-fiber-knockout drugs open up the possibillity to medically influence the afferent limb of the abnormal micturition reflex in patients with an upper motor neuron lesion. Capsaicin is an effective drug in patients with spinal cord injuries and multiple sclerosis. However, it has significant side effects. Resiniferatoxin is far more potent than capsaicin but supposedly has few side effects.

Botulinum-A toxin. Another alternative to prevent acetylcholine stimulated detrusor contractions is to block the release of this neurotransmitter from bladder post-ganglionic parasympathetic neurons. Botulinum-A toxin is a selective blocker of acetylcholine release from cholinergic nerve endings. Recently, injection into the detrusor muscle of 200–300 units of botulinum-A toxin have been reported. Under cystoscopic control the substance was injected in 20–30 different sites. It was shown that this treatment increases the maximal cystometric capacity and the volume at which the first hyperreflexive contraction occurs. It also decreases the maximal detrusor pressure in hyperreflexic patients. Although the patients were continent for several months, they needed CIC to empty the bladder because of a significant increase of post-void residual urine.

Dorsal rhizotomy of the sacral nerve roots is also able to abolish detrusor hyperreflexia at the expense of the necessity to (self)catheterize.

Neuromodulation

Non-invasive or minimally invasive electrical stimulation is available through intravaginal or anal plug electrodes and penile band electrodes. The posterior tibial nerve and the sacral dermatomes have been stimulated using TENS patches.

There is no doubt that various non-invasive stimulation protocols can result in inhibition of detrusor overactivity in patients with hyperreflexia. Convincing evidence comes from acute experiments and studies with short follow-ups. The nerve that is most often used is the pudendal nerve or its branches. The mechanism of action is based on stimulation of sensory afferent nerve fibers. These afferents probably synapse with inhibitory interneurons which connect with the parasympathetic motor neurons of the bladder. Disadvantages are the necessity to repeat the stimulation sessions on a regular basis: this is time consuming and expensive. Sacral nerve neuromodulation with an implantable electrode coupled to a pulse-generator provides the possibility to continuously stimulate relevant nerves. Studies of the Interstim device in patient with multiple sclerosis and partial spinal cord injuries have resulted in significant improvements of urinary incontinence.

Condom catheter

Condom catheters can be used in male patients when it has not been possible to achieve continence with other conservative measures like medical treatment with or without the addition of clean intermittent catheterisation.

Neurostimulation

Conservative treatment fails in some patients with a hyperreflexive bladder with or without concomittant detrusor sphincter dyssynergia. Failure may include persistent incontinence, frequent recurrent urinary tract infections caused by residual urine or deterioration of the upper urinary tract.

In such patients implantation of a Brindley sacral anterior root stimulator (bladder pacemaker) may be an option. This procedure involves dorsal rhizotomy of the sacral nerve roots which converts the hyperreflexive bladder into an areflexive bladder with a high compliance. The second part of the procedure involves placement of electrodes on the anterior sacral roots in order to be able to stimulate the roots involved in bladder contraction. Women, for whom there are no good urinary collecting devices, have more to gain from such a procedure than men.

Treatment for the hyposensitive detrusor during the filling phase
There are some small (poor quality) studies that seem to indicate that *intravesical electrical stimulation (IVES)* can improve bladder sensation, contractility and conscious control in patients with incomplete lesions to the neural pathways governing the voiding reflex. These studies need confirmation from a wider range of centers.

Treatment for the low compliance bladder during the filling phase
Medical treatment with *anticholinergics* as previously described can be contemplated. Studies of the specific effects of these drugs on decreased bladder compliance are however not available. If the decrease in compliance is due to the neurologic problem and not to scarring of the bladder wall then it seems to be logical to try anticholinergic drugs. However, in most cases of severe urological problems due to decreased compliance it is necessary to pursue surgical solutions. Surgical solutions for the low compliance bladder include bladder augmentation or enterocystoplasty, bladder autoaugmentation or detrusor myectomy and variants of urinary diversion. Clean intermittent (self) catheterization becomes necessary in about half of the patients undergoing a bladder augmentation.

Treatment for the incompetent sphincter during the filling phase
The most successful treatment for an incompetent sphincter during the filling phase is surgical treatment. The artificial urinary sphincter has been widely used in patients with neurogenic causes of sphincteric incompetence. In female patients pubovaginal sling procedures or variants thereof may be effective. If surgical treatment is not feasible or contraindicated it is necessary to either use *incontinence pads* or use appliances like *condom catheters* in male patients. *Penile clamps* are generally not recommended for long term use because of the risk of complications to the skin and urethra. Medical treatment for the incompetent striated sphincter is not available.

Voiding phase
Treatment for the underactive or acontractile detrusor during the voiding phase.

Triggered voiding can be tried in patients with an underactive detrusor. However, significant amounts of residual urine usually remain in the bladder.

Bladder expression is contraindicated if high pressures occur in the bladder during this manouvre. During the Credé manouvre the urethra kinks at the level of the pelvic floor thus creating a functional obstruction leading to high pressures.

Clean intermittent (self)catheterisation is the recommended way to empty the bladder in those with significant amounts of residual urine due to underactivity of the detrusor or overactivity of the sphincteric mechanism during the voiding phase.

An indwelling catheter should be avoided if at all possible. However, sometimes indwelling catheterisation may be the only practical solution for patients who are not able to empty their bladders themselves and who have no easy access to nursing care to perform these activities for them. A suprapubic catheter is preferred in patients with an underactive or acontractile bladder. In those with an overactive bladder it is better to try a transurethral catheter first. In case of suprapubic catheterisation leakage via the urethra often continues to occur particularly during episodes of urinary tract infection.

Treatment for the overactive sphincter during the voiding phase
Clean intermittent (self)catheterisation can improve emptying of the bladder because it by-passes the overactive spincteric mechanism.

Medical treatment to decrease the activity of the overactive closure mechanism can be contemplated. *Baclofen* which is a striated muscle relaxant is used quite widely. However, a clinically significant effect on the striated sphincter is rarely seen with a dosage schedule

that is practical. In ambulatory patients with multiple sclerosis a negative effect on the mobility is often seen long before a relevant effect on the sphincteric mechanism is found.

If a detrusor-bladder neck dyssynergia can be demonstrated during a video-urodynamic study, it may be worthwhile to try an *alpha-blocker* to improve bladder emptying.

In severe cases of detrusor sphincter dyssynergia not responding to medical treatment an endoscopic surgical sphincterotomy can be contemplated.

Treatment for bladder storage problems that are secondary to the neurologic disease but not to neurogenic bladder dysfunction
Patient with neurologic diseases and neurogenic bladder dysfunction often have decreased mobility and in many cases spent a significant part of the day in a wheel chair. The lack of "pumping" activity of the calf muscles is one factor that leads to slowing of the venous back flow and consequently to fluid retention in the lower part of the body. If the patient lies down during the night, the retained interstitial fluid is mobilised and a significant fluid load is offered to the kidneys and bladder. The storage capacity of the neurogenic bladder is then challenged to its maximum often leading to incontinence. Fluid retention during the day time can be decreased by the use of *elastic stockings* and the judicious use of *diuretics*. In some cases where night time incontinence is a more or less isolated problem *desmopressin* can be tried.

Epidemiology of Erectile Dysfunction

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Introduction

Erectile dysfunction in men represent a significant source of emotional and relationship dissatisfaction, and have a significant negative impact on the quality of life. A few decades ago, most clinicians believed that the cause of erectile dysfunction was largely psychogenic. However, it has become clear recently that erectile and other sexual dysfunctions in men are associated with a number of biological, medical, and psychological risk factors and increase markedly with aging. Complete inability to achieve an erection is relatively rare below the age of 65 years, but the majority of men over 70 years are likely to suffer from some form of erectile dysfunction. In addition to ageing, other risk factors for erectile dysfunction include chronic illnesses, various medications and cigarette smoking. Therefore, it is generally recognised that the aetiology of most erectile dysfunction is due to a combination of organogenic and psychogenic factors.

Accurate determination of the prevalence of erectile dysfunction has been difficult to estimate because the men being treated represent only a small proportion of the affected population. Epidemiological data from the 1940's and 1950's suggested that fewer than 5 million men worldwide had erectile dysfunction. However, recent studies have shown that this condition currently affects as many as 152 million men worldwide. This difference is due to improved knowledge of the anatomy and physiology of erection, which has also opened a new avenues for diagnostic and therapeutic options. Indeed, epidemiological studies provide valuable data on disease, drug and psychological variables associated with erectile dysfunction, some of which are modifiable. Elimination of these modifiable risk factors, such as cigarette smoking, alcohol consumption and certain medications, could have a significant impact on the prevalence of erectile dysfunction and consequently, the cost of its management.

Prevalence of erectile dysfunction

Prevalence data from population-based surveys indicate that results are dependent on the definition used for erectile dysfunction, the period of data retrieval and the population surveyed. The first extensive epidemiological study of male sexual behaviour was carried out in the United States in 1948 by Kinsey and colleagues. Their survey included 15,781 men 10 to 80 years old, although only 4,108 of these men were older than 25 years and only 306 were older than 55 years. Kinsey and colleagues concluded that the prevalence of erectile dysfunction was less than 1 % in men younger than 30, less than 3 % in those younger than 45, 25 % in those 65 and up to 80 % in those 80 years old. However, due to the small numbers of older men, the prevalence estimates determined by this study for men older than 55 years need to be interpreted with caution.

Since 1949 various studies investigated the prevalence of erectile dysfunction in small samples of men. In studies with community samples the prevalence of erectile dysfunction was 4 to 9 %, but the prevalence rate increased to 35 % in men aged 60 years or older. More recently, the Massachusetts Male Aging Study was conducted from 1987 to 1989 in 11 randomly selected cities and towns in the area of Boston, Massachusetts. Based on subject responses to a self-administered sexual activity questionnaire, the prevalence impotence of all degrees of 52 % as outlined below.

Community-based epidemiological studies

It has been estimated that the prevalence of erectile dysfunction of all degrees is approximately 50 % in men aged 40 to 70 years, with higher rates in those older than 70 years. Recent surveys suggest that 35 % of men aged 40 to 70 years report moderate to severe erectile dysfunction, but the overall incidence of erectile dysfunction is even higher. The Kinsey survey, which was generally regarded as the first major population-based study of erectile dysfunction in the United States, reported the prevalence to be 6.7 % among men younger than 55 years and 25 % in those older than 65 years. However, most of recent assumptions about the prevalence and incidence of erectile dysfunction are based on the analysis of data from the Massachusetts Male Aging Study, which started in 1987. This was a cross-sectional, random sample survey of health status and related issues in 1709 men aged between 40 and 70 years. In this study, 15 % of men between the ages of 40 and 70 exhibited minimal erectile impairment, 25 % had moderate impairment, and 10 % had complete impotence. In the National Health and Social Life survey, the complaint of erectile problems increased from 5–10 % in men aged 19 to 49 years to 20 % in men aged 50 to 59 years. In nationally based population survey of sexual problems, such as the American National Health and Social Life Survey, 31 % of men acknowledged at least one sexual problem in the previous year.

Community-based surveys in other countries have detected similar incidence figures to those reported by the American studies. Among middle-aged Danish men (aged 50 years), the prevalence of erectile dysfunction was reported to be 40 %. Similarly, results from a Dutch study reported that minor degrees of erectile dysfunction were common in Dutch men 50 to 78 years old, but significant dysfunction was less common (less than 5 %). An epidemiological survey of a representative population sample of 4489 men aged 30 to 80 years in Cologne, Germany reported a prevalence rate of 19.2 %, with a steep age-related increase (2.3 to 53.4 %). Similar population-based survey of 789 British men reported a prevalence of 34 %. The prevalence of erectile dysfunction in French men age 18 to 70 years is 39 % (including 11 % with permanent erectile dysfunction). This rate increases with age to 52 %. A study of 2,010 Italian men detected erectile dysfunction in 12.8 %. The prevalence increased with age from 2 % in men aged 18–39 years to 48 % in men older than 70 years. The overall incidence of erectile dysfunction in Brazilian men was reported as 46.2 % (mild in 31.5 %, moderate in 12.1 %, and complete in 2.6 %). Similarly, the prevalence of moderate or sever erectile dysfunction in Japan is 1.8 % for ages 23 to 29 years, 2.6 % for ages 30 to 39 years, 8.6 % for ages 40 to 49 years, 20 % for ages 50 to 59 years, 41.8 % for ages 60 to 69 years, and 64.3 % for ages 70 to 79 years.

In addition to the urban-based studies listed above, population-based surveys have confirmed that the prevalence and determinants

of erectile dysfunction among rural inhabitants were similar to men living in urban areas. For example, the overall prevalence of erectile dysfunction among men aged 50 to 76 years old in rural Central New York State was 46.3%. Age, perceived state of health and socio-economic status were found to be important determinants of erectile dysfunction among this population. Nationwide projections from the Massachusetts Male Aging Study suggest that erectile dysfunction could affect up to 18 million men in the United States alone. Data from the National Ambulatory Medical Care Survey indicate that there were 1.3 million office visits for erectile dysfunction in the United States in 1996. Worldwide projections from the Massachusetts Male Aging Study suggest that there will be 170 million more men aged 40–79 years with erectile dysfunction in 2025 than there were in 1995, assuming that the natural history of the condition does not change.

Risk factors and incidence of erectile dysfunction

A number of biological factors have been linked to erectile dysfunction. In addition to age, other risk factors include hormone levels, depression, diabetes, cardiovascular disease, alcohol abuse, medications, and general poor health. Results of the Massachusetts Male Aging Study indicated a higher probability of erectile dysfunction in association with certain treated medical conditions. After adjusting for patient age the probability of complete erectile dysfunction was 39% in men with treated heart disease, 28% with treated diabetes and 15% with treated hypertension versus 9.6% in the entire population surveyed. Untreated peptic ulcer, untreated arthritis and untreated allergy with probabilities of 18, 15 and 12%, respectively, also demonstrated an association with erectile dysfunction.

Despite the important role of organic conditions, the risk of erectile dysfunction is influenced by psychological risk factors. In the Massachusetts Male Aging Study after age adjustment, men with the highest levels of anger suppression and anger expression had higher probabilities of moderate (35%) and complete (16 to 19%) erectile dysfunction than the overall study population (9.6%). In addition, indexes of personality dominance and depression correlated with erectile dysfunction. Men with highest levels of dominance had lower probabilities of moderate (15%) or complete (7.9%) erectile dysfunction, whereas men with the maximum degree of depression had a higher probability of moderate or complete erectile dysfunction (90%) when compared with those who were least depressed (25%). Moreover, erectile dysfunction may be influenced by socio-cultural variables, which measure an individual's socioeconomic and normative position relative to other people. Deterioration in economic position, indexed by falling household income, is generally associated with a modest increase in risk of erectile dysfunction for men.

Specific risk factors associated with erectile dysfunction

Diabetes mellitus: Diabetic men have more than 3-fold increased prevalence of erectile dysfunction compared with non-diabetic men. The overall incidence of erectile dysfunction in diabetic men is about 20%. The incidence of erectile dysfunction increases with advancing age (10-fold higher for ages 70 to 79 years than for 19 to 29 years), duration of diabetes (1.6-fold higher with more than 10-year history of diabetes), and deteriorating metabolic control (1.7-fold higher for haemoglobin A1c greater than 9%). Moreover, the incidence of erectile dysfunction appears to be higher in type–2 than in type–1 diabetes (approximately 75 versus 45 cases per 1,000 person-years). The relative risk is 1.75 for associated obliterative arterial disease of the lower legs, 2.02 for ischemic heart disease, 1.97 for renal disease, 1.86 for peripheral neuropathy, 1.52 for retinal disease, and 3.79 for diabetic foot. Of these risk factors, the duration of diabetes, renal disease and hypertension are known to be reasonably good predictors of erectile dysfunction within the following 3 years.

Cardiovascular diseases: Erectile dysfunction has a high prevalence among male hypertensive men. This seems to be related to penile arterial vascular changes, probably atherosclerosis, although drugs used for the treatment of hypertension may also cause erectile dysfunction as discussed below. In comparison with non-hypertensive men, the odds ratio for erectile dysfunction is 1.4 (95% confidence interval 0.7–3.2) for hypertensive men. Other cardiovascular diseases are also common causes of arteriogenic erectile dysfunction, mainly through interference with the penile arterial blood flow. The prevalence of erectile dysfunction is 59% in elderly men who had had a previous heart attack when compared with 35% of those with no history of heart attacks. In the Massachusetts Male Aging Study, the age-adjusted probability for complete erectile dysfunction was 39% in men with treated heart disease, compared to 15% in untreated hypertensive patients and 9.6% in the total cohort.

Local pelvic causes: Trauma, irradiation or surgery involving the pelvic region frequently cause erectile dysfunction. Dysfunction induced by pelvic trauma can be due to the injury itself or surgical procedures for repair. External beam radiation therapy in patients with localized prostate cancer has been reported to cause erectile dysfunction in at least 25% of those treated. Erectile dysfunction is also associated with urological surgery for benign conditions of the prostate. For example, the incidence of erectile dysfunction in patients who undergo transurethral prostatectomy is 13%. Even in those who retain potency following transurethral prostatectomy, 57% will experience a decrease from preoperative levels of function. However, it is important to recognise that patients who undergo transurethral resection often erroneously equate retrograde ejaculation with erectile dysfunction.

Neurological disorders: The incidence of erectile dysfunction in men with multiple sclerosis may be as high as 65%. Erectile problems are also common in cerebrovascular diseases, and have been reported in more than 60% of men following stroke. Similarly, sexual activity and function are detected in the majority of patients with Parkinson's disease. A recent epidemiological survey reported the prevalence of erectile dysfunction in men with Parkinson's disease (mean age of 65 years) to be 60%, compared to 37.5% in aged-matched men without Parkinson's disease. The majority of men with spinal cord injured men with upper motor neuron lesions have reflex erections. However, these erections are often not adequately sustained for sexual intercourse.

Drug therapy: Various medications and substances of abuse are commonly associated with erectile dysfunction. The incidence of drug related erectile dysfunction may be as high as 25%. Drugs that may cause erectile dysfunction include certain antihypertensive medications, hormones, antidepressants, tranquilizers, alcohol, tobacco, heroin and cocaine. The incidence of erectile dysfunction in patients receiving various types of antihypertensive drugs was examined in the Treatment of Mild Hypertension Study, a 4-year, double-blind, placebo controlled trial of hypertensive subjects treated with placebo or 1 of 5 antihypertensive drugs (acebutolol, amlodipine, chlorthalidone, doxazosin and enalapril). Data analysis at 24 months revealed that the incidence of complete erectile dysfunction ranged from 2.8% in the doxazosin (alpha-blocker) group to 15.7% in the chlorthalidone (diuretic) group compared with 4.9% in the placebo group. The incidence of an mild to moderate erectile dysfunction ranged from 4.2% in the doxazosin group to 17.1% in the chlorthalidone group versus 6.8% in the placebo group.

Smoking and alcohol: The probability of erectile dysfunction in organic diseases is further increased in patients who smoked cigarettes. For instance, the probability of complete erectile dysfunction in the Massachusetts Male Aging Study was 21% in non-smoking individuals with treated heart disease compared with 56% in smokers with treated heart disease. However, the probability of complete erectile dysfunction in the entire population was not significantly different in smokers (11%) and non-smokers (9.3%). The effect of cigarette smoking on the prevalence of erectile dysfunction was further evaluated in a cross-sectional survey of 4,462 male military veterans 31 to 49 years old. The odds ratio of the association between cigarette smoking and reported erectile dysfunction was 1.5 (95% confidence interval 1.0 to 2.2) after adjusting for age, race, marital status, vascular disease, psychiatric disease, hormonal factors and substance abuse. Cigar smoking and passive exposure to cigarette smoke also significantly predicted incident erectile dysfunction. In addition to

tobacco, epidemiological studies have presented convincing evidence for an association between alcohol consumption and erectile dysfunction. The incidence of erectile dysfunction in alcoholic men is 54 %, compared with 28 % in age-matched men with no alcoholic problems.

Evaluation of circadian rhythms of autonomic parameters in neurodegenerative diseases: a useful tool for research and clinical practice.

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Daily biological rhythms are universal phenomena, encompassing a range of activities as diverse as nitrogen fixation in cyanobacteria and the sleep-wake cycle in humans. The recognition that such rhythmicity is synchronized to the periodic alternation of day and night undoubtedly dates to prehistory, but the realization that these rhythms are an innate feature of organisms is much more recent. Today the notion of internal time is generally accepted, and the study of biological timekeeping is at a fertile stage: it involves levels of biological organization from transcriptional regulation in single-cell organisms to the possible effects of jet lag on sports teams; recruits a wide array of disciplines and methodologies; and unites a host of investigators from plant geneticists to clinical neurologists. The practical importance of human circadian rhythmicity, as well as its consequences for human health and disease, are only now being realized.

Localization and Structure of Circadian Pacemakers

The biological substrates responsible for circadian timekeeping are gradually being identified. There is now strong evidence (mostly but not exclusively in rodents) that the suprachiasmatic nucleus (SCN) in the anterior part of the hypothalamus is both necessary and sufficient for the generation of circadian rhythmicity in mammals. The human SCN has been identified by immunohistochemical and receptor autoradiographic techniques, and damage to this region of the human hypothalamus can result in disturbed rhythmicity. Exciting developments in the molecular genetics of simpler organisms have led to the identification of several molecules essential to clock function. Recent experimental data showed that the SCN is linked to a diverse range of sympathetic and parasympathetic motor pathways and suggest that it is a universal autonomic timekeeper.

Human Circadian Organization

A host of daily rhythms of biological parameters has been catalogued in humans. They exhibit distinctive waveforms and temporal sequences, their phases are stable and reproducible with respect to time of day, and they are regulated through a complex interaction of circadian and noncircadian influences.

Body temperature is the rhythm most easily measured longitudinally in individual subjects and has been commonly used as a phase reference marker for the human circadian pacemaker. Body temperature usually peaks in the early evening and reaches a minimum during the latter half of the night. It is also influenced by habitual rest-activity rhythm, exercise, and ambient temperature. In general, sleep and circadian influences contribute about equally to the normal amplitude of the temperature rhythm.

Daily rhythms appear to be important factors in the expression and pathophysiology of disease, as demonstrated for asthma and cardiovascular disease.

A post-awakening morning peak has been observed for ischemic stroke (roughly between 6:00 AM and 12:00 PM). Onset of intracerebral hemorrhage is also more likely at this time, whereas a similar rhythm for subarachnoid hemorrhage has been recorded only in hypertensive (but not normotensive) individuals. These time-dependent cerebrovascular risks have been correlated with morning increases in blood pressure, heart rate, and circulating catecholamine levels; decreased fibrinolysis and increased platelet aggregation; and altered vasomotor reactivity.

Other neurological conditions exhibit daily symptomatic rhythms.

The Role of the Autonomic Nervous System (ANS) in Thermoregulation

In mammals, thermoregulatory responses to changes in body or ambient temperatures are controlled by hypothalamic preoptic integrative mechanisms that drive subordinate brainstem and spinal somatic and autonomic mechanisms. The ANS is a fundamental agent in the control of body core temperature (BcT). In particular, its sympathetic division regulates heat loss and conservation at the level of heat exchangers by inducing thermoregulatory vasomotion, piloerection and (in humans) sweating. This autonomic division also regulates metabolic heat production by skeletal muscle (shivering thermogenesis) and catabolic catecholaminergic mechanisms (non-shivering thermogenesis of brown adipose tissue). The central control of thermoregulation, like other autonomic, neuroendocrine and behavioral responses critical for homeostasis, is regulated by the central autonomic network (CAN), an internal regulation system of the brain.

The Circadian Rhythm of Body Core Temperature (CRT) as a Marker of ANS Function

The CAN is likely to regulate circadian variations in BcT translating and transmitting to the effectors the 24-hour oscillations generated by the biological clock.

Therefore the study of CRT in controlled conditions may reflect the function of the circadian oscillator and of these central autonomic structures that effectively produce the daily BcT oscillations.

Methodological Aspects

For an accurate evaluation of CRT, continuous recording of BcT by means of a portable device (Mini-logger) gives detailed information on the rhythm. The sleep-wake cycle can be monitored at the same time by an ambulant polygraphic recorder recording electroencephalogram (EEG: C3-A2, C4-A1), electro-oculogram (EOG), electrocardiogram (ECG) and electromyogram (EMG). For good control of exogenous factors the patients live in a temperature- and humidity-controlled room (24 ± 1°C, 40–50 % humidity) during the study, lie in bed except for eating, and are exposed to a controlled light-dark schedule (dark period: 23.00 h – 07.00 h). The diet can be controlled by placing the subjects on a 1800 kcal/day diet divided into three meals (08.00 h, 12.00 h, 18.00 h) and three snacks (10.00 h, 16.00 h, 22.00 h). A habituation period of 48 h in the same room and with the light-dark schedule and the diet described is recommended before the start of the recording session.

For the analysis of rhythmicity, the evaluation of the time series for BcT with the single cosinor method by means of a computerized procedure is a useful technique. This procedure determines whether or not there is a rhythm within a 24 h period ($p < 0.05$) and evaluates the following parameters with their 95 % confidence limits: (a) mesor (midline estimating statistic of rhythm): rhythm-adjusted 24 h average; (b) amplitude: difference between the maximum value measured at the acrophase and the mesor in the cosine curve; (c) acrophase: lag between reference time (24.00 h) and time of highest value of the cosine function used to approximate the rhythm.

The sleep stages can be scored according to the criteria suggested by Rechtschaffen and Kales considering epochs of 2 min to synchronize sleep-wake evaluation and temperature data. Sleep parameters such as total sleep time (TST), percentage of sleep time from 22.00 h to 07.00 h, and duration and percentage with respect to TST of each sleep phase can be evaluated applying an automatic sleep stager corrected by hand scoring.

The CRT in Neurodegenerative Diseases

Multiple System Atrophy (MSA) and Idiopathic Parkinson's Disease (IPD)

Neuropathologically, Multiple System Atrophy is characterized by cell degeneration and gliosis in the striatum substantia nigra, Purkinje cell layer of the cerebellar cortex, pontine nuclei and inferior olives. In almost all patients with autonomic failure (AF), whether they had Pure Autonomic Failure (PAF) or MSA, there was an up to 80% reduction in the number of sympathetic preganglionic neurons in the intermediolateral cell columns of the spinal cord. Brainstem abnormalities have also been noted including the dorsal nucleus of the vagus, the locus coeruleus and the nucleus of the tractus solitarius.

The clinical presentation in patients with MSA with AF is highly variable, at least at the onset of the disorder: patients may present with parkinsonism poorly responding to levodopa, with a cerebellar syndrome, with progressive AF (postural hypotension, defective sweating, failure of erection in males, constipation), or with a variable combination of these syndromes.

To evaluate whether the circadian rhythm of BcT can differentiate MSA from IPD we studied the CRT in these two groups of patients. We demonstrated that the physiological nocturnal fall of BcT is blunted in MSA patients mainly because the BcT did not decrease during sleep. This CRT pattern is not justified by difference in sleep structure and may reflect an impairment of central sympathetic nervous system function. The pathological basis of this thermoregulatory defect could be the abnormalities in the ventrolateral medulla and in the SCN recently demonstrated in the brains of patients with MSA.

Fatal Familial Insomnia (FFI)

Fatal familial insomnia is an autosomal dominant disease clinically characterized by untreatable insomnia, dysautonomia and motor signs. The histopathological hallmark of FFI is a severe atrophy of the thalamus, especially of the anterior ventral and mediodorsal nuclei, associated with a variable involvement of the inferior olives, striatum and cerebellum.

A 24-hour oscillation persisted in FFI patients, but profound alterations of the CRT always appeared with disease progression. The mesor progressively increased concurrent with decrease in the acrophase; the acrophase was shifted in most studies.

Thus the progressive increase in mesor and the respective decrease of amplitude seem to be determined by the prevalence of neurogenic mechanisms for heat production over those responsible for heat dissipation that try to balance the system with a relative hyperactivity. Therefore in those cases where short episodes of NREM persist, BcT, blood pressure and heart rate fall abruptly but still display a normal state-dependent behavior. From the chronobiological point of view, FFI offers a unique opportunity to observe the daily patterns of autonomic and hormonal parameters in human subjects independent of the sleep-wake cycle. The persistence of an albeit impaired CRT after months of total agrypnia confirms the presence of an endogenous oscillator regulating BcT circadian variations independently of the sleep-wake cycle.

The 24-hour oscillation of blood pressure and heart rate in MSA and IPD

24-hour non invasive blood pressure (BP) and heart rate (HR) monitoring is a useful technique for the investigation and evaluation of cardiovascular autonomic abnormalities. In normal subjects, BP is usually higher in the day and lower when the subject is asleep at night. In MSA, an altered control of BP with a "non dipper" circadian profile was described. Two mechanisms were hypothesized: a nocturnal blood volume expansion due to a fluid shift from the extravascular component to blood vessels or a vasoconstrictor model based on evidence of a denervation hypersensitivity of the vascular α-adrenergic receptors. A possible impairment of the central oscillator has never been addressed.

Methodological aspects

BP and HR need to be continuously monitored non invasively by a Portapres portable device. In patients with autonomic failure, we prefer to avoid ambulant recording and we apply the same protocol already described in the CRT section. In this controlled setting for the evaluation of BP and HR variations related to food intake, subjects passed from supine to sitting position and after 5 min from sitting to standing position for 5 min. This change in body position was repeated 10 min before and 30 min after breakfast, lunch and dinner. For a good interpretation of the data, patients should be drug-free and diabetes, alcoholism, amyloidosis and thyroid dysfunction should be excluded by appropriate investigations.

The data obtained in a 24-hour recording can be analysed by classical chronobiological statistics (cosinor method) or evaluating the state-dependent changes – namely the mean values of BP and HR during wakefulness and different sleep stages. For this purpose, the sleep-wake cycle must be monitored simultaneously using an ambulant polygraphic recorder.

With this methodology we demonstrated that the 24-hour profile of BP appears normal in IPD and altered in MSA again suggesting an impairment of the central timekeeper in MSA. Interestingly, no alteration of the circadian rhythm of HR was found in either group.

Moreover, the state dependent variations of these autonomic parameters were preserved in IPD and impaired in MSA in which postprandial orthostatic hypotension and nocturnal hypertension frequently occur.

From Research to Clinical Practice

A critical amount of information on the chronobiology of patients with neurodegenerative diseases has been accumulated in the last decade leading to practical applications not only in human physiology and pathology but also in the treatment of diseases. The time domain has become an essential part of the analysis of any physiological process.

The recognition of temporal abnormalities of BcT, BP and HR associated with MSA represent a useful tool for adapting the appropriate treatment to specific patients. For instance, for dysautonomic patients living in temperate climates, heat intolerance is not usually the most prominent symptom but can be an insidious disorder leading to life-threatening heat stress disorders during summer and in hot and humid environments. The evaluation of CRT may be a useful tool for the diagnosis of thermoregulatory failure in neurodegenerative diseases, permitting the identification of patients with heat intolerance and the application of preventive measures to avoid hyperthermia. The study of 24-hour BP profile allows the diagnosis and evaluation of the circadian distribution of BP dysregulation. This information is useful in the choice and timing of administration of pharmacological treatment and yields practical suggestions like fractioning of food intake into frequent small meals with a reduced carbohydrate content to reduce postprandial hypotension or the intake of a high carbohydrate snack with a moderate amount of alcohol before nocturnal sleep to prevent supine hypertension.

In conclusion, the evaluation of circadian rhythms of autonomic parameters in neurodegenerative diseases is a useful tool in the diagnosis and follow-up of patients. It may give important physiopathological suggestions on the role of the ANS in the circadian timing system function, allowing an optimisation of non-pharmacological and pharmacological treatment of dysautonomic patients.

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The vestibulo sympathetic reflex in humans

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It has been proposed that a vestibular reflex originating in the otolith organs modulates sympathetic activity during changes in posture with regard to gravity. We recently tested this hypothesis (Exp Brain Res 2002) by selectively stimulating otolith receptors sinusoidally along different head axes in the coronal plane with off-vertical axis rotation (OVAR) while recording sympathetic efferent activity in the peroneal nerve (MSNA). We found that blood pressure, respiratory rate and MSNA entrained at the frequency of rotation, with MSNA increasing in nose-up positions and decreasing when nose-down. MSNA correlated closely with blood pressure when within ± 90°of nose-down positions with a delay of 1.38 s, which is the normal latency of baroreflex-driven MSNA changes. Thus, in the nose-down position MSNA was driven by baroreflex afferents. In contrast, within ± 45°of the nose-up position, MSNA was closely related to gravitational acceleration at a latency of 0.6 s. This delay is too short for MSNA changes mediated by the baroreflex, but is compatible with the delay of a sympathetic response originating in the otoliths. Hence, a vestibulo-sympathetic reflex, probably originating in the otolith organs, contributes to blood pressure maintenance during forward linear acceleration. Because of its short latency, this reflex may be the earliest mechanism to maintain blood pressure upon standing.

The otolith organs sense head position with regard to gravity and initiate compensatory ocular and postural reflexes. In the cat, these receptors also regulate sympathetic efferent activity, which contributes to blood pressure maintenance. To test whether vestibulo-sympathetic reflexes are present in humans, we stimulated otolith receptors along different head axes with off-vertical axis rotation and recorded sympathetic efferent activity with a miniaturized microneurography device. During off-vertical axis rotation, blood pressure, respiratory rate and sympathetic efferent activity to skeletal muscle (MSNA) were periodically modulated at the frequency of rotation, with MSNA increasing in the nose-up position and decreasing when nose-down. MSNA was closely correlated with blood pressure when nose-down with a latency of 1.38 s, indicating that, in this position, it was driven by baroreflex afferents. MSNA was tightly correlated with the gravito-inertial acceleration vector during the nose-up position at a latency of 0.6 s and was not affected during transient voluntary apnea. Hence, there is a vestibulo-sympathetic reflex in humans that contribute to blood pressure maintenance during forward linear acceleration, such as experienced upon standing.

Stretch receptors in the vascular wall (baroreceptors) regulate sympathetic vasoconstrictor activity to blood vessels in skeletal muscles. In the cat, the vestibular apparatus contributes to this activity; pitch of the head increases sympathetic activity in the splanchnic nerves [1] and transection of the vestibular nerves results in hypotension during head up tilt [3]. In humans, a vestibulo-sympathetic reflex would be particularly useful upon standing, since tilt of the head would induce circulatory adjustments before vascular stretch receptors detect volume changes.

To measure sympathetic efferent nerve activity during gravitational changes induced by sinusoidal linear acceleration along various head axes, we used a miniaturized microneurography device, developed for the Neurolab Space Flight (STS-90) [4]. We monitored blood pressure, heart rate, respiration and sympathetic postganglionic nerve activity (muscle sympathetic nerve activity, MSNA) in the peroneal nerve during constant velocity, off-vertical yaw axis rotation (OVAR). During experiments, subjects were seated upright and rotated in darkness at constant angular velocities of 24, 60 and 110°/s, either about an earth-vertical axis (EVAR) or about an axis tilted 15° from the vertical (OVAR). This corresponds to frequencies of rotation of 0.067, 0.167 and 0.306 Hz. During OVAR, a gravity vector of 0.26-g circled the head in the direction opposite to that of rotation. In the steady state, this selectively stimulated only the otolith organs, not the semicircular canals [5, 6]. By averaging cycles of rotation during OVAR, we detected the effects of linear acceleration along specific head axes [7, 8]. EVAR, which does not stimulate the otolith organs, provided a control. Data were collected during EVAR and OVAR in the steady state after per-rotatory nystagmus had disappeared.

During EVAR, there was no discernible pattern in MSNA bursts associated with the frequency of rotation (Fig. 1A). In contrast, bursts of sympathetic nerve activity appeared during each cycle of OVAR at all three velocities (Fig. 1B-D). The spectrum of MSNA had peaks at the heart rate [9] (Fig. 2, solid arrows) both during EVAR and OVAR. During OVAR, strong spectral peaks appeared in the MSNA at each frequency of rotation (Fig. 2B-D). At 110°/s, there was also a peak at the second harmonic (0.61 Hz) of the rotation frequency (Fig. 2D), which varied among subjects.

Within each cycle of rotation, bursts of sympathetic activity consistently occurred when the subjects were close to the "nose-up" position (Fig. 1B-D). The correlation between the increase in MSNA and the nose-up position was present in all seven subjects (Fig. 3D, E). Changes in blood pressure, R-R intervals and respiratory rate (Fig. 3A-C), were also closely linked to the rotation rate (Fig. 3E). Although changes in blood pressure were small, pressure was lower at the nose-up than the nose-down position (Fig. 3C). Respiratory rate also tended to be entrained at the rotation frequency, with maximum chest expansion occurring in the nose-down position (Fig. 3A).

To distinguish between changes in MSNA driven by the linear acceleration sensed by the otoliths from those due to changes in respiratory rate, we asked the subjects to stop breathing at the end of expiration over several cycles of rotation. Peaks of MSNA still occurred (Fig. 1E), indicating that changes in MSNA during OVAR were not secondary to changes in ventilation.

To determine whether changes in MSNA during OVAR were driven by baroreflexes, we plotted ΔMSNA as a function of systolic blood pressure (SBP), obtaining a complex Lissajous pattern (Fig. 4A). A Lissajous pattern close to a straight line indicates that the temporal cross-correlation between the two variables is maximal, and a circular pattern indicates a 90° phase shift with a temporal cross-correlation of zero. Elliptical patterns are associated with phase shifts of less than 90° and less than optimal correlations [10]. In peroneal nerve recordings, the latency of changes in MSNA caused by changes in blood pressure is 1.22–1.54 s [9]. Advancing ΔMSNA by an approximate mean of 1.38 s to account for this latency, yielded a strong linear relationship between ΔMSNA and systolic blood pressure during the half cycle when the nose was down (Fig. 4A, left). This accounted for 83 % of the variation in ΔMSNA, suggesting that changes in MSNA in this half cycle were mainly due to changes in blood pressure. In contrast, there was a considerable phase shift between systolic blood pressure and ΔMSNA when the nose was up (Fig. 4A, right). The two were not significantly correlated during this half of the cycle, indicating that the baroreflex afferents were not driving ΔMSNA in nose-up positions.

To determine whether linear acceleration along the naso-occipital axis ($A_H(x)$) was driving sympathetic efferent activity, we plotted ΔMSNA vs. $A_H(x)$ (Fig. 4C). Otolith afferent activity encodes head tilt with regard to gravity as well as head linear acceleration [11]. The vector sum of head acceleration and gravity, termed gravito-inertial

acceleration is used by the vestibular system to generate the perception of vertical as well as adequate ocular and postural reflexes. With an appropriate phase delay between signals to account for the conduction delay to the peroneal nerve and for signal filtering, portions of the Lissajous pattern were close to a straight line when the nose was up (right panel, Fig. 4B). The tightest fit for the linear relationship between ΔMSNA and $A_H(x)$ occurred with delay of 0.6 s when the head was moving within ± 45° from the nose up position (Fig. 4B, inserts). The linear regression in this region accounted for 96 % of the variation in MSNA. Subtracting 0.2 s introduced during processing of the MSNA signal (see Methods), the actual transmission time from the vestibular system to the peroneal nerve was estimated at 0.4 s. Changes in MSNA and AH(x) were not correlated when the nose was down. Hence, in nose-up positions, MSNA increases according to the nasooccipital linear acceleration vector, suggesting that graviceptors modulate sympathetic efferent activity.

These data indicate that directionally sensitive otoliths are the likely source for the short latency increase in MSNA that occurs when sensing forward linear acceleration. Such linear acceleration occurs when the head moves forward and upward, e. g., when standing up. Thus, a "feed-forward" mechanism in humans, as in the cat [1], produces autonomic adjustments at the beginning of movements that are likely to induce gravitational stress on the circulatory system. Such a mechanism would trigger cardiovascular adjustments prior to the baroreceptor reflex, which is only recruited after alterations in homeostasis have already occurred.

The entrainment of respiratory rate to the frequency of OVAR confirms recent studies showing that pitch-sensitive otolith afferents also modulate nerve activity to respiratory muscles [12, 13]. Such modulation would also serve to induce appropriate adjustments in respiratory function during movements in a gravitational environment.

Methods

Seven normal healthy subjects (five males and two females) participated in this experiment. Their ages ranged from 17 to 33 years (mean 28.8). The Institutional Review Board (IRB) approved the experiment and subjects signed consent forms prior to participation. Blood pressure, heart rate (R-R intervals), MSNA, respiratory rate and eye movements were monitored during yaw rotation in a clockwise direction (to the subjects' right) in darkness for six minutes around an earth-vertical axis (EVAR) or around an axis tilted 15° from the vertical (OVAR). The head was fixed to the chair and the body was restrained during rotation. Data were taken 50 s after the onset of rotation, after the per-rotatory nystagmus had disappeared, so that the responses were in the steady state. The semicircular canals are activated during the angular acceleration at the onset of EVAR and OVAR, but during steady state rotation do not contribute further to the response since they signal zero velocity. The otoliths are not stimulated during EVAR. During OVAR at 15° tilt, a rotating gravity vector of 0.26-g circles the head in the direction opposite to that of rotation and selectively activates otolith and somatic afferents (termed otolith afferents) sinusoidally at the frequency of rotation. Frequencies of rotation were 0.067 Hz (24°/s), 0.167 Hz (60°/s) and 0.306 Hz (110°/s).

Eye movements were monitored with a video-based system (ISCAN, Cambridge MA) at a frame rate of 60Hz. Sympathetic activity in the right leg was measured with a recording electrode placed in the peroneal nerve (microneurography of muscle sympathetic nerve activity, MSNA) with a miniaturized microneurography apparatus originally developed for the NASA Neurolab mission. This system utilized a preamplifier with a 100-fold gain, containing redundant 100 μA current limiters to prevent leakage of current through the reference or recording electrodes. Total amplification was 70 to 160 k. The signal was rectified and integrated at a time constant of 0.1 sec. The technique of microneurography is detailed elsewhere [14].

The ΔMSNA signal was the percent difference between the integrated MSNA over a 0.1s interval and average integrated MSNA for that interval, based on a given cycle. The ΔMSNA signal oscillated about an average value of zero over the cycle. Data from 10 consecutive cycles were averaged for each subject. This method could have introduced an additional delay of up to 0.1 s. Thus, the total processing delay of the ΔMSNA was up to 0.2 s. This value (0.2 s) was subtracted from the optimal delay that determined the most linear Lissajous patterns when correlating ΔMSNA and naso-occipital linear acceleration.

Continuous blood pressure monitoring was based on the volume clamp method with finger plethysmography (Portapres, TNO, Amsterdam, Netherlands). Respirations were monitored with impedance, using elastic bands placed around the thoracic and abdominal regions, connected to a selective gain amplifier and a summing box (Respitrace Ambulatory Monitoring, Ardsley, New York).

Data collection used a WinDaq/Pro+ software (Dataq Instruments, Inc, Akron Ohio). Analog data were digitized online with an eight-channel analog-to-digital converter card (National Instruments Corporation, Austin, Texas) at a sampling rate of 500 Hz. Custom-written software was used for data analysis. ECG data was processed according to the Berger algorithm and treated with a low pass filter at 40 Hz. Time series were treated with a linear interpolation filter set at 300 ms for R-R interval. All parameters were analyzed for their mean values and power spectra density (Blackman-Tukey spectral type with linear detrending, at 4 Hz resolution). A 256 s wide data window was used for spectral analysis so that spectral frequencies as low as 0.015 Hz could be reliably analyzed.

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Urogenital disorders in spinal cord disease

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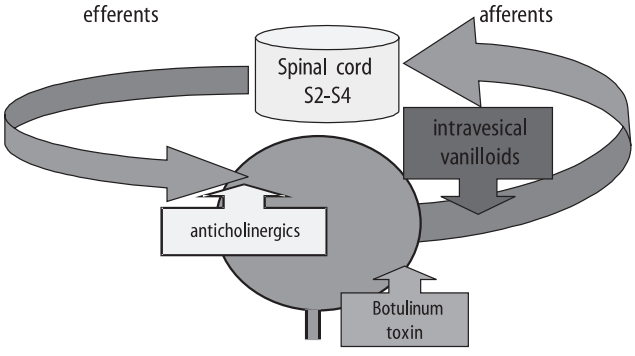
Immediately following spinal cord injury (SCI) those injured ask "Will I walk again"? However, often within a year or so, reconciled to their inability to walk, their predominant concerns are to do with pelvic organ function i. e. bladder, bowel and sex and this is the same for patients who suffer chronic, progressive spinal cord disease, such as multiple sclerosis. All three pelvic organs will function due either to preserved or emergent segmental reflexes but the problem is of volitional control.

Loss of voluntary defecation is a major worry to patients with spinal cord injuries. Studies have shown that difficulties with bowel evacuation are rated amongst the most serious problems following spinal cord injury. At present there is little that can be offered.

The bladder dysfunction which results from spinal cord injury is due to the disconnection from the pontine micturition centres. It is at that level in health, that the synergistic behaviour of the striated sphincter and the detrusor muscle is co-ordinated so that during detrusor contraction, sphincter relaxation occurs. Following spinal cord injury, detrusor sphincter dyssynergia with the possible development of upper tract dilatation is a serious complication. Furthermore the bladder is likely to develop hyperreflexia due to the emergence of a sacral segmental reflex that causes involuntary bladder contraction in response to low bladder filling. This dysfunction can be specifically counteracted by the use of intravesical vanilloids (Fig. 1). Currently detrusor injections of botulinum toxin appear to be a promising treatment.

Fig. 1 Emergent segmental reflex causing hyperreflexia following SCI and sites of action of drugs



The genital sensory experiences of sexual activity are inevitably lost or impaired by spinal cord disease but reflex erections are likely to be preserved since these are subserved by sacral segmental reflexes. Sildenafil citrate *(Viagra)* which enhances any form of sexually stimulated erection has proved to be particularly effective in the treatment of men with spinal cord injury or multiple sclerosis.

Postural tachycardia syndrome – an update

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Introduction/Definition: Orthostatic hypotension is well-recognized but is relatively uncommon. For every patient seen with orthostatic hypotension there are approximately 5–10 patients with orthostatic intolerance, defined as the development, on standing up, of symptoms of cerebral hypoperfusion (e. g. lightheadedness, weakness, blurred vision), associated with those of sympathetic activation (such as tachycardia, nausea, tremulousness), and an excessive heart rate increment (≥ 30 bpm). Female:male ratio is about 4–5:1 and most case occur between the ages of 15 and 50 years.

Clinical Features: We evaluated the autonomic symptom profile in a large cohort of patients with POTS using a single standardized instrument (Sandroni et al. 1999). This approach permits the definition of the prevalence and distribution of autonomic failure including orthostatic intolerance. We evaluated a total of 108 POTS patients using a structured and validated autonomic symptom profile, consisting of 167 questions encompassing 10 autonomic categories of symptoms (orthostatic intolerance; sexual dysfunction; bladder dysfunction; diarrhea; gastroparesis; secretomotor disorder; sleep disorder; constipation; vasomotor; pupillomotor). Fifty percent of patient has an antecedent viral illness. Most (78 %) patients had the disorder for less than 5 years. The symptoms were frequent or persistent (64 %) and at least moderately severe in 57 % and either unchanged or getting worse in 93 % of patients at presentation. Positive family history of similar complaints occurred in 25 %. The following orthostatic symptoms occurred in > 75 % of subjects: Lightheadedness/dizziness, lower extremity or diffuse weakness, disequilibrium, tachycardia, shakiness. These symptoms were most commonly aggravated by heat, meals and exertion and occurred most commonly at no particular time of day. Other autonomic symptoms were dry eyes or mouth, gastrointestinal complaints of bloating, early satiety, nausea, pain and alternating diarrhea and constipation. We concluded that patients with POTS at presentation have severe, persistent symptoms of orthostatic intolerance, but may also have involvement of other autonomic systems, especially gastrointestinal. Fatigue is a significant complaint in about half the patients. Episodic, non-orthostatic symptoms of autonomic surges are common.

Quality of Life: Dr Benrud-Larson in a study of 94 patients (89 % female, mean age = 34.2) at the Mayo Clinic evaluated quality of life (SF-36) and symptom severity (Autonomic Symptom Profile). Compared to a healthy population, patients with POTS reported impairment in multiple domains of quality of life, including physical, social, and role functioning. Hierarchical regression analyses revealed that symptom severity ($\beta = -0.36$, $p < 0.001$) and disability status ($\beta = -0.36$, $p < 0.001$) were independent predictors of the SF-36 physical component score, with all variables accounting for 54 % of the variance [$F(5, 72) = 18.0$, $p < 0.0001$].

Evidence of Peripheral Denervation: POTS is heterogeneous; some patients have a limited, presumably immune-mediated autonomic neuropathy. An antecedent viral infection and evidence of peripheral denervation occurs in approximately 50 % of patients. On thermoregulatory sweat test or QSART, anhidrosis of the legs are commonly found. Peripheral adrenergic denervation is present. Evidence includes loss of phase II_L of the Valsalva maneuver; reduced lower extremity secretion of norepinephrine when compared with the upper extremity. Perivascular round cell infiltration is sometimes seen on nerve biopsy, and ganglionic antibody is occasionally positive, especially in the more severely affected patients. Loss of epidermal fibers is sometimes seen on skin biopsy. As a result of peripheral denervation, capillaries have been suggested to be excessively leaky, in children with POTS, and hypovolemia develops with continued standing. We recently demonstrated excessive splanchnic pooling,

presumably due to partial denervation of splanchnic-mesenteric venous capacitance bed.

Other Pathophysiologic Studies: A mutation in the norepinephrine transporter has been reported (Shannon et al. 2000) but is rare. In a study of 80 patients no such mutation was found. In a pharmacologic study on adrenergic tone, Jacob et al. (2000) demonstrated that there was an increase in adrenergic tone, evidenced by the change in BP following ganglion blockade. They demonstrated no evidence of peripheral receptor sensitivity in this study, and ascribed the increase to central mechanism. Sandroni et al. (2000) undertook a pharmacologic dissection of the Valsalva maneuver. We found that POTS patients had mean phases, when compared with controls, that were characterized by more negative II + E ($p = 0.07$), smaller II ± L ($p = 0.04$), and significantly larger phase IV ($p = 0.001$). The intravenous infusion of 10 mg phentolamine in controls resulted in a pattern mimicking those of patients with POTS at baseline. Propranolol significantly reduced phase IV in both controls ($p < 0.05$) and in patients with POTS ($p < 0.001$) and improved the headache symptoms, when present, during and after phase IV. The authors conclude that phase IV is mainly under β-adrenergic regulation and that the exaggerated phase IV in POTS is a result of a hyperadrenergic state. Cerebral hypoperfusion is due to an increase in cerebral vasoconstrictor tone, in part due to hypocapnia. In a study of 30 patients with POTS (Novak et al. 1998) we found that the POTS group had greater reductions in, pulse pressure ($p < 0.01$) and CO_2 ($p < 0.001$), and that total systemic resistance failed to increment. Among the cerebrovascular indices, all blood flow velocities (systolic, diastolic, mean) fell significantly more, and cerebrovascular resistance (CVR) were increased in POTS patients ($p < 0.01$) compared to controls. In both groups, hyperventilation induced mild tachycardia ($p < 0.001$), significant reduction of BFV and a significant increase of CVR associated with a fall in CO_2. Hence cerebral vasoconstriction occurs in POTS during orthostasis, which in significant part is due to hyperventilation, causing significant hypocapnia, reversible by CO_2 rebreathing. When cerebral autoregulation is rigorously studied (obviating the confounding effects of changes in critical closing pressure) no changes in actual arteriolar regulation was found. We measured the resistance area product (RAP) of cerebral vascular resistance, calculated on a beat-to-beat basis from the slope of the best linear fit between the upstroke of the raw signal of BP and CBFV of each cardiac cycle. An autoregulatory index (ARI) was then calculated as the slope of the linear fit between beat-to-beat values of RAP and MBP during the VM. A higher ARI stands for a greater change of RAP with the same change of BP and therefore better CA. The slope was unchanged in POTS.

Follow-up: On follow-up, 80 % of patients were improved, 60 % were functionally normal, and 90 % were able to return to work, although some symptoms persisted (Sandroni et al. 1999). Patients who had an antecedent event appeared to do better than those with spontaneous POTS. Salt supplementation and beta-blockers were the most efficacious therapies. We concluded that in the majority of patients, POTS is self-resolving, especially in those with a triggering event.

Management: A variety of approaches have been used to alleviate symptoms in POTS. All patients need volume expansion and a high salt-high fluid regimen. Drugs reported to be of benefit include midodrine, propranolol, clonidine, and phenobarbital. Other measures used include body stockings and physical countermaneuvers. These treatments may influence pathophysiologic mechanisms of POTS such as alpha-receptor dysfunction, beta-receptor supersensitivity, venous pooling, and brainstem center dysfunction. We prospectively studied hemodynamic indices and symptom scores in patients with POTS who were acutely treated with a variety of interventions. Twenty-one subjects who met the criteria for POTS were studied (20 women, 1 man; mean age, 28.7 ± 6.8 years). Patients were studied with a 5-minute head-up tilt protocol, ECG monitoring, and noninvasive beat-to-beat blood pressure monitoring, all before and after the administration of an intervention (intravenous saline, midodrine, propranolol, clonidine, or phenobarbital). Patients used a balanced verbal scale to record any change in their symptoms between the tilts. Symptom scores improved significantly after the patients received midodrine and saline. Midodrine and propranolol reduced the resting heart rate response to tilt ($p < 0.005$) and the immediate and 5-minute heart rate responses to tilt ($p < 0.002$). It was concluded that midodrine and intravenous saline are effective in decreasing symptoms on tilt in patients with POTS when given acutely.

Pyridostigmine: We investigated 18 patients (15 female, 3 male, 18–44 years, mean-age 28.7 years) with POTS. Autonomic failure was quantified by distribution and severity reaching 2.4 ± 1.3 on a composite autonomic severity scale (CASS) from 0 to 10. HR, blood pressure (BP) and indices for cardiac output (COI), enddiastolic volume (EDVI) and peripheral resistance (PRI) were continuously monitored during supine rest and during 5 min of 70 degree head-up tilt before and one hour after oral application of 60 mg pyridostigmine (Mestinon™). Plasma catecholamines (Norepinephrine (NE), Epinephrine (E), Dihydroxyphenylglycol (DHPG)) were determined for the supine and upright position before and after medication. Patients scored orthostatic symptoms on a symptom-scale from 0 to 10 for both tilts. Pyridostigmine significantly reduced HR in both supine (78.9 ± 11.5 vs. 73.0 ± 11.1bpm, $p < 0.001$) and upright position (123.7 ± 17.8 vs. 110.6 ± 17.0bpm, $p < 0.001$). The HR-increase with tilt was significantly blunted (44.8 ± 16.6 vs. 37.6 ± 10.1bpm, $p < 0.05$). No significant differences were seen for other cardiovascular parameters. The changes of HR were associated with improvement in orthostatic symptoms: Symptom-score pre-drug: 5.6 ± 2.9, post-drug: 4.2 ± 2.7 ($p < 0.01$). NE increased after medication for both supine (pre-drug: 214 ± 96, post-drug: 263 ± 131pg/ml, $p < 0.05$) and upright position (pre-drug: 491 ± 246, post-drug: 552 ± 278pg/ml, $p < 0.01$) No side effects were reported. We concluded that Pyridostigmine improves orthostatic tolerance in orthostatically intolerant patients without inducing significant side effects. The presumed mechanism is improvement of sympathetic ganglionic transmission along with the known cholinergic properties of this drug. If placebo-controlled studies can confirm these findings pyridostigmine can be a new useful tool in the treatment of OI.

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Poster Session 1: Thursday, May 16, 2002, 16.00–17.00

P1) Sympathetic baroreflex activation increases pupil size

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The factors influencing the physiological regulation of the pupil size in humans are not fully known. Animal studies suggest an influence of mechanical changes (e. g. induced by changes in arterial blood pressure) as well as of brainstem structures (e. g. baroreflex-mediating neurons) on the variation of the pupillary diameter (PD).

In this study, we evaluated whether cardiovascular sympathetic activation has an effect on PD in humans.

At baseline and during autonomic challenge induced by oscillating lower body negative pressure (LBNP) at –40 mmHg in 11 healthy young persons (4 male, 7 female, 20–28 years old), we continuously monitored RR-intervals (ms), mean blood pressure (BP) (mmHg) [Pilot™, Colin], respiration [Respitrace™, Ambulatory Monitoring, Inc.] and PD [V-CIP1.0/1.1™, AMTech] for 125s after 30 minutes adaptation to an ambient light intensity of 120 lux. After removal of blink artifacts, we measured the mean pupil size (mm). Additionally, we calculated mean RR-intervals, mean BP and spectral power of the RR-interval (ms^2) and BP modulation ($mmHg^2$) in the low (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.50 Hz) range at baseline and during autonomic challenge.

During oscillating 0.1 Hz lower body negative pressure, mean PD increased significantly from 4.83 ± 0.23 mm to 5.51 ± 0.20 ($P < 0.05$). Mean RR intervals decreased from 952 ± 24 ms to 884 ± 25 ms ($p < 0.05$) but mean blood pressure did not change significantly. Spectral power of mean BP in the LF range increased ($P < 0.05$) from 2.04 ± 0.65 $mmHg^2$ to 3.47 ± 0.80 $mmHg^2$.

Our data show increased PD during sympathetic challenge by lower body negative pressure. We hypothesize that activation of medullary baroreflex function mediating neurons is conveyed to central structures modulating the pupil size. Further studies will address the value of pupillary monitoring for differentiation between patients and controls during sympathetic challenge.

P2) The BK channel β1 subunit gene is important to baroreflex function in man

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The baroreflex, which is important for the minute-to-minute regulation of blood pressure and heart rate, is influenced by genetic variance. Ion channels are important to baroreflex afferent and efferent function. Mice missing the β1 subunit of the $Ca2^+$-sensitive potassium channel (BK) are hypertensive and have a reset baroreflex. We tested the hypothesis that variants in the gene (KCNMB1) coding for the BK β1 subunit is associated with baroreflex function. We studied 6 single nucleotide polymorphisms (SNPs) in KCNMB1. Heart rate variability and baroreflex function were calculated at rest in 88 monozygotic twin pairs and in 61 dizygotic twin pairs. Four SNPs in intron 3, exon 4a, exon 4b, and exon 4c gave significant results. For instance exon 4b SNP AA individuals had higher heart rate variability, compared to CA, or CC persons in particular in the high frequency range. The low frequency range showed no association. Consistent with the heart rate variability data, homozygous AA persons had greater baroreflex slopes than CA or CC persons, also in the high frequency range. These associations could not be shown in the low frequency range for heart rate variability and baroreflex slopes. These data support the notion that variants in channel genes may be responsible for the great variation in heart rate variability and baroreflex function observed in man. Such variation may also play a role in the development of cardiovascular diseases.

P3) Dendrodendritic contacts and dendritic bundles in human basolateral amygdala

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The amygdaloid complex and hypothalamus are the most important neuronal systems for regulation of vegetative functions. The amygdala also play role in the storing of implicit emotional memory, especially the one related to fear conditions. The most interesting finding of dendrodendritic contacts (DDC) in nonhuman studies are the reciprocal dendrodendritic synapses between the mitral and granule cells shown in the accessory olfactory bulb of the pregnant female mouse. In those studies DDC participate in the olfactory recognition memory formed to male pheromones by a female mouse at mating.

The aim of our study was to examine morphology of the dendritic neurons in the human basolateral amygdala. It was performed on preparations impregnated by the Golgi technique of 12 adult postmortem brains (24 hemispheres), of both sexes (6 male and 6 female), aged 30–65 years.

The analysis of the dendritic branches on our preparations has shown an occasional presence of DDC and dendritic bundles (fascicular dendritic arrangement). Dendritic bundles represent grouping of the dendrites with predomination in the parvicellular division of the basal nucleus and paralaminar nucleus. We have found the presence of dendrodendritic contacts, indicated by the light microscopy. DDC were especially frequent in the parvicellular division of the basal nucleus as well as in the paralaminar nucleus.

According to our results DDC vary as to their complexity, ranging from connections involving two neurons to joint dendritic contacts originating from four to five neurons. The complex morphology of dendritic neurons in the human basolateral amygdala and the presence of the dendrodendritic contacts are important because of their possible role in vegetative and emotional processes in which amygdala have a leading position.

P4) Expression of nicotinic acetylcholine receptor α-subunits in developing rat heart

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Nicotinic acetylcholine receptors are ligand-gated ion channels with a pentameric structure and a central ion pore. They consist of different subunits. The presence of transcripts coding for α2 – α7 and α9 neuronal nicotinic acetylcholine receptor subunits was investigated using reverse transcription polymerase chain reaction (RT-PCR). RNA was isolated from rat heart on prenatal days 14, 16, 18 and 20, postnatal days 3, 8, 10 and 30, and in adults. The results indicate that α3, α4, α5, α7 subunit mRNAs are expressed from prenatal day 14 continuously throughout all tested stages, whereas α2 subunit mRNA was present from prenatal day 20. The α6 subunit was only transiently expressed from prenatal day 14 to postnatal day 8, but absent on post-

natal day 30 and in adult hearts. However, a clear positive signal for α9 nAChR subunit mRNA has not been obtained in any tested developmental stages.

Additionally, immunohistochemistry was used to establish the distribution of α4 and α7 subunits throughout the heart. Cardiomyocytes, as well as smooth muscle cells, were immunoreactive for both antibodies in all tested developmental stages. Intracardiac neurons were labeled only with antiserum against α7 subunit.

RT-PCR revealed that multiple α subunits occur during development, and that there is a shift of α6 to α2 subunits of nicotinic receptor occurring at the time of delivery. Immunofluorescence showed that nicotinic receptors of the neuronal types are located on the surface of both cardiomyocytes and other cell types, and both cellular and subcellular distribution changes in the course of ontogeny and postnatal maturation of the rat heart.

P5) Cross-talk between catecholaminergic and sensory neurons in the rat heart

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The present study was aimed to reveal putative developmental interrelationships among three types of neurons within the cardiac plexus: sympathetic adrenergic neurons, small intensely fluorescent (SIF) cells and sensory neurons. After birth, animals were subjected to sympathectomy by guanethidine, sensory denervation by capsaicin and combined sympathetic + sensory denervation. Intact rats served as controls. The origin of neurons was examined by fluorescent immunohistochemistry. Specific antibodies raised against tyrosine hydroxylase (TH), dopamine β-hydroxylase, phenylethanolamine N-methyl transferase, neuropeptide Y and calcitonin gene-related peptide (CGRP) were applied to whole-mount atrial preparations of 20- to 40-day-old rat. Individual neurons were identified by means of the general neuronal marker protein gene product (PGP 9.5) and the synaptic vesicle antigen synaptophysin (p38). At the age of 40 days, concentrations of noradrenaline (NA), adrenaline (A), dopamine (DA) and CGRP were determined in tissue extracts of right and left atria (RA, LA) using commercial radioimmunoassay method and expressed in ng/g wet weight. In control rats, NA and A concentrations were higher in RA than LA, whereas DA levels were higher in LA than RA, suggesting multiple neuronal origin of DA. Sympathectomy led to at least 95% reduction of NA and A concentrations in the atria while DA levels decreased only slightly. Thus the SIF cells, strongly immunoreactive for DA-synthesizing enzyme TH, seem to be unaffected by guanethidine. In contrast, sensory denervation caused a significant increase in all catecholamine concentrations in both atria. While DA levels increased 6–8 fold, NA and A concentrations augmented by factors 1,2–1,9 only. In conclusion, sensory innervation may have inhibitory effect on the development of the sympathetic postganglionic neurons. Removal of the sensory input to SIF cells seems to increase DA concentrations independently on NA and A levels in both atria.

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P6) Baroreflex buffering and susceptibility to vasoactive drugs

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Background. The overall effect of vasoactive drugs on blood pressure is determined by a combination of the direct effect on vascular tone and an indirect baroreflex-mediated effect. Differences in baroreflex function affect the responsiveness to vasoactive medications, particularly baroreflex buffering of blood pressure; however, the magnitude is not known. *Methods.* We characterized baroreflex function and responses to vasoactive drugs in different degrees of baroreflex dysfunction namely patients with idiopathic orthostatic intolerance, patients with essential hypertension, patients with monogenic hypertension and brachydactyly, multiple system atrophy patients, and in control subjects. We used phenylephrine sensitivity during ganglionic blockade as a measure of baroreflex blood pressure buffering. *Results.* Phenylephrine 25 μg increased systolic blood pressure 6 ± 1.6 mmHg in control subjects, 6 ± 1.1 mmHg in orthostatic intolerance patients, 18 ± 3.9 mmHg in patients with essential hypertension, 31 ± 3.4 mmHg in patients with monogenic hypertension, and 25 ± 3.4 mmHg in multiple system atrophy patients. Similar differences in sensitivities between groups were observed with nitroprusside. The sensitivity to vasoactive drugs was highly correlated with baroreflex buffering function and to a lesser degree with baroreflex control of heart rate. In controls, sensitivities to nitroprusside and phenylephrine infusions were correlated with baroreflex control of heart rate and sympathetic nerve traffic. *Conclusion.* Our findings are consistent with an important effect of baroreflex blood pressure buffering on the sensitivity to vasoactive drugs. They suggest that even moderate changes in baroreflex function may have a substantial effect on the sensitivity to vasoactive medications.

P7) Mechanisms of sympathetic activation by adenosine

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The direct vasodilatory and negative chronotropic effects of adenosine in humans are counterbalanced by a reflex increase in sympathetic nerve traffic. Suggested mechanisms for this reflex include peripheral chemo- and baroreceptor activation.

Aim: To assess the relative contribution of peripheral chemoreceptor activation to the increase in muscle sympathetic nerve activity (MSNA) by adenosine.

Methods: Finger arterial pressure (Finapres) and MSNA (microneurography) were recorded during steady state infusion of adenosine (140 microgram/kg/min, 5 min) in five patients that had lost carotid chemoreflex function due to bilateral carotid body tumor resection (BCBR, 1m:4f, 51 ± 11 years) and in 6 healthy controls (2m:4f, 50 ± 7 years). MSNA responses to sodium nitroprusside injections were assessed for the estimation of baroreceptor mediated sympathetic activation.

Results: In response to adenosine, controls show no significant change in systolic/diastolic blood pressure (+1.1 ± 2.6/–2.1 ± 2%), a +48.2 ± 13.2% increase in heart rate ($p = 0.003$) and a +195 ± 103% increase in MSNA total amplitude/minute ($p = 0.022$). In contrast, BCBR patients showed a decrease in systolic/diastolic blood pressure of –14.6 ± 4.9/–17.6 ± 6% ($p < 0.05$) an increase in heart rate of +25.3 ± 8.4% ($p = 0.032$) and no significant increase in MSNA (+63.1 ± 30.8%). Hypotension during adenosine infusion in the individual BCBR patients elicited a smaller increase in MSNA than did equihypotensive doses of sodium nitroprusside.

Conclusions: Absence of carotid body chemoreflex function following BCBR results in abolishment of a significant MSNA response to continuous adenosine infusion. Carotid chemoreceptor activation is essential for the prevention of vasodilation by adenosine. Blunting of the baroreflex mediated MSNA response to adenosine-induced hypotension suggests a sympatho-inhibitory effect of adenosine on ganglionic neurotransmission.

P8) Selective norepinephrine reuptake inhibition prevents tilt-induced vasovagal reactions

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Background. The mechanism of vasovagal syncope is poorly understood. Some studies suggest that excessive adrenergic stimulation of the heart may trigger vasovagal reactions (ventricular hypothesis). Norepinephrine transporter inhibition increases cardiac adrenergic stimulation and promotes orthostatic tachycardia. *Methods.* In a double-blind crossover study, 24 healthy subjects (12 men, age 29 ± 1 yrs, BMI 22.7 ± 0.5 kg/m^2) ingested 8 mg of the selective norepinephrine transport blocker reboxetine or placebo 12 hrs and 1 h before testing. Brachial blood pressure, finger blood pressure and heart rate were measured continously. After reaching a stable baseline in the supine position, subjects were tilted gradually, with an increment of 15°each 3 min. Subject remained at 75° head-up tilt (HUT) for 30 min or until symptoms developed. Blood pressure and heart rate responses of the last 5 min of head-up tilt testing were evaluated by two blinded investigators. *Results.* Reboxetine raised supine heart rate (69 ± 5 compared to 64 ± 3 bpm with placebo, $p < 0.05$) and blood pressure (122 ± 5/71 ± 1 compared to 109 ± 4/63 ± 1 mmHg with placebo, $p < 0.01$). At 3 min 75° HUT heart rate was 85 ± 3 bpm with placebo and 120 ± 3 bpm with reboxetine ($p < 0.001$). With placebo 18 tilt tests were aborted due to orthostatic symptoms. With reboxetine only 6 tests were terminated prematurely. Mean tilt duration was 30 ± 2 min with placebo, and 37 ± 2 min with reboxetine ($p < 0.01$). With placebo 14 subjects experienced vasovagal reactions (58 %), compared with one subject on reboxetine (4 %, $p < 0.001$). *Conclusion.* Increased cardiac adrenergic stimulation induced by selective norepinephrine transporter inhibition prevents vasovagal reactions during head-up tilt testing in healthy subjects. This observation challenges the ventricular hypothesis for vasovagal syncope. Instead, norepinephrine transporter blockade might be a useful treatment of vasovagal syncope.

P9) Blood pressure variability in AT_2 receptor disrupted mice

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Acting through the AT_1 receptor in the central nervous system, angiotensin II has effects on autonomic pathways regulating cardiovascular function. The role of the AT_2 receptor is less well understood. We tested the hypothesis, that the AT_2 receptor is involved in autonomic vascular regulation.

Therefore, we investigated heart rate variability (HRV) and the spontaneous baroreflex sensitivity (BRS) in AT_2 -/- (n = 8) and in AT_2 +/+, (n = 7) mice. We employed telemetry and adapted sequence analysis from humans to the mouse for this purpose. Data analysis was performed off-line for two hours segments (8 to 10 a. m.). HRV and BRS (cross spectra) were analyzed during 5 minutes of stationary data in the time and frequency domain (coefficient of variation, CV, standard deviation, SD, HF-power: 1.0–3.0, LF-power: 0.25–0.60, and VLF-power: 0.015–0.250 Hz).

Mean arterial pressure was 103 ± 3 mm Hg in AT_2 -/- mice and 101 ± 2 mm Hg in AT_2 +/+ mice. Mean pulse interval was 128 ± 5 ms in AT_2 -/- mice and 123 ± 4 ms in AT_2 +/+ mice. HRV tended to be higher in AT_2 -/- (CV: 8.5 ± 1.3 vs. 6.1 ± 0.7; HF-power: 25 ± 10 vs. 9 ± 3 ms^2). Systolic blood pressure variability in the LF band was markedly lower in AT_2 -/- (LF-power: 0.6 ± 0.1 vs. 4 ± 1.3 mm Hg^2). Baroreceptor-heart rate reflex sensitivity, calculated with the sequence technique, was 3.2 ± 0.3 in AT_2 -/- and 2.1 ± 0.3 ms/ mm Hg in AT_2 +/+ ($p < 0.05$).

Our data supports the hypothesis of an inhibitory central effect of the AT_2-receptor in respect to baroreflex function.

P10) Adrenergic reactivity and heart rate variability in healthy subjects

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Aim: To study the prognostic value of adrenoreactivity index as an indicator of peripheral sympathetic nervous system activity.

Material: Thirty healthy subjects aged 27.1 years on an average were included in the study.

Methods: Adrenergic reactivity was evaluated using the index of beta-adrenergic reception of cell membranes (beta-ARM). Spectrum analysis of heart rate variability (HRV) was carried out in conditions of rest and during active orthostatic testing (AOT).

Beta-ARM method is based on changes in red blood cells RBC osmotic resistance caused by a beta-adrenoceptor blocker. In healthy subjects, values of beta-ARM fall within a range of 2 to 20 arbitrary units. According to this method, decrease in the value of beta-ARM is accompanied by increase in sensitivity of peripheral beta-adrenoceptors in conditions of decreased concentration of catecholamines, and vice versa.

Results: Values of beta-ARM in the studied subjects fell within the physiological normal range of 5 to 20 a. u. Analysis of these indices in groups with extreme ranges of beta-ARM values (5 to 9 and 17 to 20 a. u.) was carried out with the aim to reveal the most typical differences in HRV indices.

In the group of healthy subjects with high sensitivity of peripheral beta-adrenoceptors (5 to 9 a. u.), activity of sympathetic nervous system (SNS) was low in conditions of rest and increased by 20 minutes of AOT. In the group with lower sensitivity of beta-adrenoceptors (beta-ARM = 17 to 20 a. u.), peripheral vegetative mechanisms were equilibrated in conditions of rest, but development of additional activation of sympathetic activity during AOT was not observed.

Conclusion: High adrenergic reactivity in conditions of rest reflects the initially decreased activity of SNS and makes it possible to predict its activation during AOT; the decreased adrenergic reactivity corresponds to initially higher SNS activity with less prominent activation during AOT.

P11) Contrasting effects of sibutramine on autonomic cardiovascular regulation

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Background. Sibutramine, a serotonin and norepinephrine transporter blocker, is widely used as an adjunctive treatment of obesity. Genetic variability in the norepinephrine transporter gene and selective pharmacological blockade elicit profound changes in cardiovascular regulation, particularly with standing. Whether or not sibutramine elicits a similar response is unknown. *Methods*. In 11 healthy subjects (7 men, age 27 ± 2 years, BMI 23.1 ± 0.7 kg/m^2), we compared the effect of 20 mg Sibutramine or matching placebo ingested 26h, 14h and 2h before testing. In addition, we tested sibutramine in combination with the beta-1 adrenoreceptor blocker metoprolol. The study was conducted in a randomized, double-blind, crossover fashion. We

determined cardiovascular responses to autonomic reflex tests and to a graded head-up tilt test (HUT). *Results*. While supine, heart rate was 62 ± 2 bpm with sibutramine, 58 ± 2 bpm with placebo and 54 ± 2 bpm with sibutramine and metoprolol. At 75° HUT, heart rate was 97 ± 3 bpm with sibutramine, 85 ± 2 bpm with placebo, and 66 ± 3 bpm with sibutramine and metoprolol ($p < 0.01$ sibutramine vs placebo), respectively. Supine systolic arterial pressure was 121 ± 3 mmHg with sibutramine, 113 ± 3 mmHg with placebo and 111 ± 2 mmHg with sibutramine and metoprolol and 120 ± 4 mmHg, 108 ± 3mmHg and 104 ± 3mmHg with sibutramine, placebo and sibutramine with metoprolol at 75° HUT ($p < 0.01$ sibutramine vs placebo). The rate pressure products, a rough estimate of myocarial oxygen consumption, was markedly increased with sibutramine and decreased with sibutramine and metoprolol. Sibutramine attenuated the blood pressure response to hand grip and cold pressor testing. *Conclusion.* In normotensive subjects, sibutramine increases resting blood pressure while attenuating the response to sympathetic stimuli. Sibutramine causes a marked increase in upright heart rate, which can be prevented with beta adrenoreceptor blockade.

P12) Cardiac and sympathetic discharge oscillatory patterns during carotid baroreflex stimulation

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Aim: To evaluate whether muscle sympathetic nerve activity (MSNA) and RR interval variability may present a functional asymmetry in response to right versus left carotid baroreceptors stimulation.

Subjects: 12 healthy volunteers (5 F, 7 M; age 32 ± 2 years)

Methods: Every subject underwent a sinusoidal neck suction (from 0 to –50 mmHg) at 0.1 Hz, applied at the right side (A), left side (B), concomitant right and left sides in phase concordance (C) and opposition (D). Respiration was controlled at 0.25 Hzr to overcome possible changes in baroreflex sensitivity induced by modifications of breathing pattern. Power spectrum analysis assessed the changes in the 0.1 Hz oscillatory component of RR interval and MSNA variability induced by the rhythmic baroreceptor loading.

Results: Mean RR interval and MSNA were unchanged during each neck suction as compared to baseline (925 ± 38 ms and 16 ± 1.7 bursts/min, respectively). The 0.1 Hz oscillatory component of MSNA increased and reached similar values in A (1.75 ± 0.28 log a. u.^{2}), B (1.77 ± 0.3 log a. u.^{2}), C (1.82 ± 0.28 log a. u.^{2}) and D (1.88 ± 0.31 log a. u.^{2}). Sinusoidal neck suction increased the power of the 0.1 Hz oscillatory component of RR variability in C (1563 ± 417 ms, $p < 0.05$), A (791 ± 160 ms) and D (826 ± 204 ms) as compared to B (550 ± 83 ms).

Conclusions: One side carotid baroreceptor stimulation did not elicit functional asymmetry in the neural sympathetic discharge activity. Conversely, right side and combined right and left sides stimulation both in phase and in opposition of phase were more effective in modulating RR variability than the left side stimulation alone. Thus, right and left carotid baroreflexes seem to modulate differently heart beat and sympathetic activity to the vessels.

P13) Baroreceptor reflex at advanced age and hypertension: the follow-up study

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Aim of the study was to evaluate the influence of advanced age and progression of essential hypertension on the baroreceptor-cardiac reflex mediated autonomic control of heart rate at rest and during pressor reaction evoked by skeletal muscle contraction.

Subjects: Age and gender matched 10 healthy controls (males, age 37 ± 7 yrs – starting observation) and 11 essential hypertension patients (stage II WHO, age 39 ± 6 yrs – starting observation) were observed repeatedly after the time period 10 years.

Methods: Beat-to-beat heart rate and finger mean arterial pressure were monitored non-invasively and heart rate reaction to baroreflex activation by neck suction (– 60 mmHg, 5 s) was analysed at rest and during handgrip with force 50 % of maximal voluntary contraction.

Results: Progression of essential hypertension after 10 yrs period is related with increase of mean arterial pressure (103 ± 3 vs. 0.116 ± 2 mmHg; $p < 0.05$), decrease of heart rate reaction to baroreflex activation at rest (6.4 ± 1.1 vs. 2 ± 0.7 bpm; $p < 0.05$) and rise of pressor reaction amplitude at handgrip cessation moment (21 ± 13 vs. 33 ± 4 mmHg; $p < 0.05$). In control group mean arterial pressure and heart rate at rest, pressor reaction amplitude at handgrip cessation moment, as well as heart rate reaction to baroreflex activation were not significantly changed, only heart rate reaction tended to be lower (12.6 ± 3.0 vs. 0.10.9 ± 3.3 bpm; NS) after the same time. At repeated observations, both in essential hypertension patients and controls, heart rate at rest and it's acceleration amplitude at handgrip cessation moment were without significant modifications, although heart rate acceleration trajectory was altered and heart rate reaction to baroreflex activation disappeared faster during the muscle effort.

Conclusions: Thus, observed peculiarities in sympatho-parasympathetic balance in autonomic control upon the sinus node at essential hypertension will be rather attributed to the progression of disease than the subject's aging.

P14) Transdermal absorption of estradiol in normal and peripheral neuropathies at different sites

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In the past it has often been stated that the permeability of the skin for drugs widely differs between different sites of the body. Autonomic and somatosensory nerves in the epidermis innervates sweat glandes, arteries and arrectores pilorum muscles. The relation of disturbed autonomic epidermis innervation to altered transdermal absorption in polyneuropathy is not yet clear.

In this study we measured serum estradiol in 29 normals (25 male, 4 female; age 54 ± 12.6 years) and 10 polyneuropathy patients (8 male, 2 female; 4 diabetic neuropathy, 2 chronic alcoholism, 2 thiamine deficiency, 2 unknown reason) to assess potential differences of estradiol uptake from different skin sites. Estraderm TTS® was administered in a randomised sequence to different sites. There was no significant difference between sites of application (subclavicular/back of the foot) in each group. The ratio of absorption subclavian to the dorsum of the foot did not differ in normals or polyneuropathy patients. Neuropathy was confirmed in all patients in the polyneuropathy group by clinical examination, diminished nerve conduction velocieties and reduced sensory nerve action potentials amplitude. Even in patients with abnormal sympathetic skin response or heart rate variability no significant difference of estradiol uptake was found at any site.

In conclusion: The transdermal resorption of estradiol is not altered in peripheral neuropathies especially with autonomic dysfunction. The application of a transdermal system at any site will result in comparable absorption. Measurement of transdermal absorption is not useful as a diagnostic tool in autonomic neuropathies.

This work was supported by the Paul Kluth-Foundation. The Ethics committee of the University of Witten/Herdecke approved the study and informed consent was obtained.

Poster Session 2: Friday, May 17, 2002, 10.30–11.30

P15) Management of the urinary bladder dysfunction after large intrapelvic operations

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Aim: To establish the functional outcome of bladder dysfunction after large intrapelvic operations for cancer, in patients with a serious compromise of quality of life due to this urologic morbidity.

Material: Between July 1996 and December 2001, 34 patients who had undergone various intrapelvic operations as a treatment for cancer, were examined by the Urodynamics Department of our Clinic. Those operations were: radical prostatectomy (no = 18), colectomy-anterior resection (no = 8), colectomy-Hartman's operation (no = 4), radical hysterectomy (no = 4). All patients reported no urinary problems prior to the operation and none of them received any neo-adjuvant or adjuvant radiation therapy.

Methods: We used clinical neurourological tests and urodynamics to assess the symptoms and the underlying pathology.

Results: We determined 14/18 sphincter damage incontinence and 4/18 cases of detrusor instability in the radical prostatectomy group of patients. Findings in the other groups were somewhat different: In colorectal surgery group we had 3 patients with detrusor instability, 4 cases of uncontractile detrusor and 5 cases of clear stress incontinence. Finally, in the post-radical hysterectomy group, 2/4 women, had stress incontinence, and the rest 2/4 had an uncontactile detrusor. Detrusor compliance seemed unaffected in every case, except of the detrusor instability diagnosis. Low sensitivity bladder (high first sensation and first urge volumes) was our finding in 17/34 cases.

Conclusions: An appropriate knowledge of bladder urinary dysfunction following large intrapelvic operations, by the use of the necessary tool of Urodynamics, should lead to both, an anatomic nerve-preserving approach during the operation, and a successful management of the occurring post-operative urinary disorders.

P16) Effect of the hypothalamic defence area on urinary bladder contractions

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The defence reaction can be evoked from the perifornical hypothalamic area and the region just dorsal to the ventromedial hypothalamic nucleus (Jordan, 1990). Stimulation of this region evokes muscle vasodilation, vasoconstriction in cutaneous and intestinal vascular beds and kidney, a rise of blood pressure and in cardiac output, increased heart rate and cardiac contractility, pupillary dilation, piloerection and rapid, shallow breathing (Jordan, 1990). Micturition occurs with an increase of the pelvic activity to the urinary bladder leading to an increase of bladder pressure and contractions and a decrease of somatic activity to the sphincter (de Groat *et al.*, 1993). The anterior hypothalamus has been implicated in the bladder control (Morrison, 1987). Some studies indicate the existence of two pathways that run through the hypothalamus that initiate bladder contractions (Morrison, 1987). In the present study, we investigate the effect of the stimulation of the hypothalamic defence area (HDA) on the pelvic nerve activity and on bladder function.

Experiments were performed in 10 female SD rats, anaesthetised (pentobarbitone, 40 mg/Kg) and paralised (pancuronium, 4 mg/Kg/h). The trachea was cannulated. Rectal temperature was maintained at 38 °C. Blood pressure (BP), ECG, bladder pressure (BlP), pelvic nerve activity (PN) and heart rate (HR) were recorded. After a craneotomy, HDA was identified (Yardley and Hilton, 1986). After this identification, 2 intensities of stimulation (50 Hz, 1 ms) were used: a higher (100–150 μA) and a lower intensity (< 30 μA). At the beginning of the experiment, the bladder was filled (8–15 cmH_2O) until small contractions (2–4 cmH_2O) were observed. Stimulation sites were marked with pontamine blue dye and identified subsequently (Paxinos and Watson, 1986). For statistical analysis the *t*-Student test for paired observations was used and values of *t* were considered significant when $p < 0.05$. All data are expressed as mean ± SEM.

HDA stimulation evoked an increase of BP from 98.5 ± 0.96 to 151.0 ± 3.16 mmHg and in BlP from 12.8 ± 0.49 to 49.6 ± 0.87 cmH_2O (n = 10). For lower intensities of stimulation (< 30 μA) it was possible to distinguish between 2 regions within HDA separated by 100–150 μm in the vertical plan: in ventral points was evoked a significant increase on BP from 103.5 ± 0.99 to 128.3 ± 1.05 mmHg) with little or no changes on BlP (from 11.5 ± 0.43 to 15.5 ± 0.42 cmH_2O) (n = 6); at dorsal sites the same stimulus intensity (less than 30 μA) elicited significant changes on BlP (from 11.2 ± 0.6 to 36.8 ± 1.7 cmH_2O) with only small rises on BP from 103.5 ± 0.76 to 112.8 ± 0.60 mmHg (n = 6).

The present study has shown that HDA stimulation is able to produce excitatory responses of bladder function with an increase on bladder pressure and bladder contractions.

All the experimental procedures were performed according to Portuguese and EU laws on animal research.

P17) Vasovagal-type response after reopening of right coronary artery (RCA) in acute myocardial infarction

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Aim Different arrhythmias have been reported to occour during reperfusion in acute myocardial infarction. We observed a transient sinus bradycardia and asystole or A-V block in some, associated with arterial hypotension instantly after reopening of RCA (rarely of LCx and never of LAD artery). We investigated this vasovagal-type response in a group of consecutive patients with acute myocardial infarction referred for primary percutaneous transluminal coronary angioplasty (PTCA).

Patients In the year 2000, primary PTCA was performed in 147 patients (101 male; age range 35–85y; mean age 62 ± 13 y). In 60 (41 %) patients infarct related artery was LAD, in 22 (15 %) LCx, in 61 (41 %) RCA in 2 it was left main and in one patient vein graft.

Results Bradycardia (≤ 45/min) and arterial hypotension (≤ 90/60 mmHg) with (pre)syncope developed in the range of seconds after reopening of the RCA (Tab. 1).

Table 1 Patients with bradycardia and hypotension after reopening of infarct related coronary artery

	LAD n = 61	*LCx* n = 22	*RCA* n = 61
Bradycardia	0	2	26 (43 %)*
Hypotension	4	1	24 (39 %)*

*$p < 0.01$

In RCA group, slow heart rate was due to sinus bradycardia in 17 (65 %) patients. Sinus asystole of more than 3 s was demonstrated in additional 6 (23 %) patients and in 3 (12 %) patients bradycardia was due to A-V block 2–3°. Bradycardia and hypotension were invariably

reversible and benign, responded to lower-body elevation, saline or coloid infusions, atropine 0.5–1.0 mg i. v., or to baloon inflation and coronary artery reocclusion. Bradycardia was reversible in the range of tens of seconds and hypotension in the range of tens of minutes.The phenomenon of tachyphylaxis was also noticed after repeated occlusion-reopening of the artery. In addition, single vessel disease and TIMI flow zero were more frequently demonstrated in patients with bradycardia and hypotension than in those without it (54 % vs. 22 %, 77 % vs. 46 %, $p < 0.02$). There was no difference in median symptom-to-baloon inflation times between the groups (248 min vs. 245 min).

Conclusions We demonstrated a vasovagal-type response instantly after reopening of RCA in acute myocardial infarction. Therefore, inferoposterolateral region of the human heart may be a chemosensitive or barosensitive reflexogenic area of the depressor reflex. Our findings suggest that neurocardiogenic concept of vasovagal syncope may be operative in at least some clinical conditions. Additional research is needed to elucidate the mechanism of this response.

P18) Cardiac autonomic control in shift-workers after interruption of the work-schedule

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Background and Aim: In habitual shift-workers we observed that, the spectral index of sympatho-vagal balance modulating the SA node activity, LF/HF, undergoes circadian fluctuations characterized by values lower at sleeping time and higher during working periods. In addition, when subjects worked at night, LF/HF was reduced compared with morning and evening working time. It is unclear whether a 30-day job interruption might shift the period of the maximum of LF/HF thus restoring the day-night oscillation observed in habitual day-workers. In addition, it is unknown whether simple day awareness without work attendance might result in values of LF/HF similar to those observed during morning and evening working periods.

Subjects: 10 healthy male, habitual shift-workers (age: 39 ± 3 years).

Methods: Every subject underwent four 24-hour EKG recordings; three corresponded to morning, evening and night work shifts and one was performed at the end of the summer vacations (day off). We compared RR interval and LF/HF values measured during the 8-hour period of work corresponding to the 3 different shifts and during the 8 a. m. – 5 p. m. period of the day off. Autoregressive power spectrum analysis was performed on RR interval variability.

Results:

	1st shift (6 a. m.– 2 p. m.)	2nd shift (2 p.m.– 10 p. m.)	3rd shift (10 p. m.– 6 a. m.)	30 Day Off (8 a. m.– 5 p. m.)
RR(msec)	758 ± 40	706 ± 37	804 ± 49	750 ± 18
LF/HF	6.7 ± 1.1	9.1 ± 1.7	5.8 ± 0.8*	6.2 ± 3.3*

*$P < 0.05$ vs 2nd shift

Conclusions: A 30-day interruption of work restored the day-night oscillations of LF/HF, marker of the cardiac sympatho-vagal modulation. Moreover, day off was characterized by values of LF/HF reduced as compared with the evening working period and not different from those observed during night work. Thus, the sympathetic activation attending night work is similar to that achieved during a day without any work performance and may greatly impact work efficiency during the night.

P19) Heart rate variability as a predictor of the outcome of head-up tilt testing

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Aim/Methods: We studied the relation between heart rate variability (HRV) and the outcome of head-up tilt testing (HUTT) in 27 patients with suspected neurally mediated syncope (NMS) (35 ± 13 years) and in 13 age-matched controls. After 15 minutes of baseline supine observation, patients were tilted to 60 degrees for 45 minutes or until syncope occurred (Westminster protocol). HRV parameters included RR intervals, standard deviation of normal-to-normal RR intervals (SDNN), and root mean square successive differences (RMSSD). HRV analysis was performed for 15 minutes during the supine position and immediately after the onset of HUTT until syncope or until the end of tilt in patients without syncope.

Results: Syncope occurred after a mean tilt duration of 25 minutes in 18 (67 %) of 27 patients with clinically suspected NMS, whereas all 13 controls had a negative HUTT. In the supine position, RR intervals and RMSSD were not statistically different among HUTT-positive patients, HUTT-negative patients, and controls (RR intervals: 790 ± 80, 803 ± 95, and 792 ± 89 ms, P = NS; RMSSD: 38 ± 30, 40 ± 31, and 43 ± 32 ms, P = NS). At the same time SDNN was also comparable in HUTT-positive patients versus HUTT-negative patients with presumed NMS versus controls (45 ± 26 vs 42 ± 20 ms vs 38±22, P = NS). In the tilt position RR intervals and RMSSD were shorter in HUTT-positive patients compared to HUTT-negative patients, or to controls (RR intervals: 580 ± 80 vs 729 ± 121 and 751 ± 93 ms, $P < 0.05$; RMSSD: 10 ± 4 vs 33 ± 12 and 37 ±27 ms, $P < 0.05$).

Conclusions: HRV analysis in the baseline supine position was not a predictor of HUTT outcome in patients with clinically suspected NMS. Patients with syncope during HUTT have an increased sympathetic activity before the event expressed by an increase in heart rate and by a decreased parasympathetic tone manifested by a decrease in RR intervals and RMSSD measurements before the event, in comparison with HUTT-negative patients and with controls.

P20) The early increase of heart rate during head up tilt testing as a predictor of a positive outcome

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Aim/methods: Two recent studies showed that an early increase in heart rate could be used as a predictor of the positive outcome of the head up tilt testing (HUTT), with a very good sensitivity and specificity. We performed passive tilt tests using the Westminster protocol in 43 consecutive patients who were clinically diagnosed with neurally mediated syncope (NMS).These patients (25 women and 18 men) had a mean age of 45 ± 19 years, did not have any other cardiac illness and did not take any drugs. Twenty-eight patients (65 %) had a positive HUTT and fifteen patients (35 %) had a negative HUTT. The early heart rate increase was defined as the average heart rate of the ten first minutes of tilting minus the average heart rate of the ten last minutes in the supine position (using a holter monitor).

Results: The early heart rate increase was significantly higher in the group of patients with positive HUTT (24.7 ± 7.1 bpm) versus the group of patients with negative HUTT (13.4 ± 4.7bpm, $P < 0{,}001$).

Conclusion: An early and stable increase of the average heart rate of about 20 bpm(best cut-off point) is a sensitive predictor of the positive outcome of the HUTT in patients with presumed NMS and no other heart disease.

P21) Prospective SNA activity for Stroke in 1000 subjects initially aged 65

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Purpose: With aging, autonomous nervous system activity decreases and, furthermore, its parasympathetic arm loses progressively its dominance. Also, it seems to be the same population who loses ANS activity, suffers hypertension and orthostatic hypotension and presents with lacunar brain images. However, a prospective study of the prognosis value of the decrease in autonomous nervous system activity over the occurrence of stroke have never been conducted. *Methods*. We will assess Heart Rate Variability (HRV) and Spontaneous Baroreflex Sensbility (sBRS) evolution in a randomized population of 1000 subjects, selected from the inhabitants of Saint-Etienne, France, initially aged 65 years old and which will be followed until they reach 72 years old. Brain imaging (RMI), carotid echo-doppler, cognitive functions and standard risk factors will alos be assessed. Examinations will be repeated five times during the follow-up. *Results:* At that time, 616 subjects entered the study. We already observed that: SDNN was · 100, 75–100, < 75 and < 50 ms in, respectively 503, 71, 16 and 0 subjects and that sBRS was = 6, 3–6, and < 3 ms/mmHg in, respectively, 317, 224 and 75 subjects. These 2 variables were correlated between each other (chi^2 $p < 0.001$) but their linear correlation coefficient was only $r = 0.38$ ($p < 0.001$). The presence of HTA was associated to a lower sBRS (6.17 ± 3.12 vs 7.17 ± 15.21, $p < 0.0015$), a lower SDNN (128.14 ± 35.88 vs 135.88 ± 33.66, $p < 0.001$) but not a lower RMSSD (ns) value. *Conclusion:* sBRS was more often severely altered (< 3 in 75 subjects) than HRV who was < 75 in 16 cases and < 50 in none. The repeated programmed measurements will help evaluate the respective predictive value of these parameters on cardiovascular events, and more particularly on stroke occurrence.

P22) Increase of baroreflex and HRV with training in the elderly

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Purpose: Autonomic nervous system activity decreases continuously with age and appears as a powerful predictor of disease and death. Thus, in the intent of improving health, attempts are made to reincrease autonomic nervous systemactivity. *Methods:* We assessed autonomic nervous system activity by heart rate variability and cardiac spontaneous baroreflex sensitivity in eleven elderly men (73.5 ± 4.2 years) before and after a 14 weeks of cycloergometer sustained interval training program. Heart rate variability indices were calculated using time domain, Fourier and wavelet analysis over 24-hour Holter recordings. Baroreflex sensitivity was calculated from 15-minute recordings of blood pressure and RR interval spontaneous variations using sequences and cross spectral methods. *Results:* After the training period, VO_{2peak} increased by 18.6% (26.8 ± 4.4 to 31.8 ± 5.2 $ml.kg^{-1}.min^{-1}$, $p < 0.01$). Total power and high frequencies of heart rate variability increased up to 73.8% ($p < 0.05$) and the BRS indices increased up to 52.5% (6.9 ± 2.2 to 10.5 ± 3.7 $mmHg.ms^{-1}$, $p < 0.05$). *Conclusion:* Intensive endurance training in the elderly increased the spontaneous cardiac spontaneous baroreflex sensitivity and more generally the parasympathetic activity. Physiological mechanisms and long-term clinical benefits on health status should be further investigated.

P23) Orthostatic hypotension – etiology, symptomatology and complications

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Background and Purpose: Orthostatic hypotension (OH) occurs in a heterogeneous group of patients with differences in etiology, degree of autonomic impairment, and symptoms. We reviewed an unselected group of patients evaluated in a uniform manner at the Mayo Autonomic Reflex Laboratory to determine the cause and characteristics of OH as well as the prevalence of anemia, supine hypertension, and hypertensive end-organ damage.

Subjects and Methods: We investigated all patients undergoing autonomic reflex testing at Mayo Clinic Rochester in 1998, whose blood pressure (BP) dropped by at least 20mmHg during head-up tilt. Patients were asked to complete an extensive symptom questionnaire. Autonomic function was quantified using a composite autonomic severity scale (CASS). Clinical notes, laboratory results and EKG were reviewed to determine the primary disorder and the frequency of complications.

Results: 127 patients with OH were included, 70 male, 57 female, mean-age 65.8 ± 14 years. The primary disorders were distributed as follows: Multiple System Atrophy (MSA): 34%, Parkinson's Disease: 10%, Pure Autonomic Failure (PAF): 8%, Idiopathic Autonomic Neuropathy: 6%, Diabetic Neuropathy (DN): 18%, Neurogenic OH (unspecified): 15%, Neurogenic POTS: 3%, other disorders: 5%. The average CASS score was 5.6 ± 2.2, indicating moderate autonomic failure; the average systolic BP drop was 43 ± 25mmHg. Supine hypertension (defined as BP ≥160/95mmHg) was present in 49% of patients, electrocardiographic signs of leftventricular hypertrophy in 7%, and anemia in 40% (83% normocytic). Orthostatic symptoms were reported in 94% of patients, most commonly dizziness (89%) and weakness (79%). Syncope had occurred in 42%. Most patients (63%) reported no circadian changes of symptoms, while in 34% symptoms were worst in the early morning. Distinct differences were noted between different patient groups. So was CASS highest in PAF and lowest in POTS, as was the orthostatic BP drop and the frequency of supine hypertension.

Conclusions: OH comprises a variety of disorders, the most common being MSA and DN. The degree of autonomic impairment varies with the underlying disorder. Syncope, supine hypertension and anemia are frequent complications of OH.

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P24) Normal values of cardiovascular reflex tests of autonomic nervous system function in Greek population

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Purpose: The assessment of cardiovascular Autonomic Nervous System *(ANS)* function is significant especially for diabetic patients. We have developed data on ANS function and the necessity for normal values in our population is imperative. This is the first time for Greek population, that we try to set normal values of cardiovascular reflex tests of ANS function. *Patients-methods:* Tests were performed in 218 healthy subjects (108 males, 110 females) with mean age 37.4 ± 10.4 years (range 21–75 years). Their age distribution was as follows: $N_1 = 64$ (21–30 years), $N_2 = 71$(31–40 years), $N_3 = 54$ (41–50 years), $N_4 = 28$ (51–60 years), $N_5 = 1$ (75 years). All subjects were healthy, off medication and with mean BMI 24.1 (range 22–27 Kg/m^2). We performed in all subjects the following 3 standard cardiovascular reflex

tests of ANS function. 1) Heart rate variation during deep breathing [analyzed by Expiration/Inspiration index *(E/I)*, Mean Circular Resultant *(MCR, vector analysis)*, Standard Deviation *(SD)*], 2) Valsalva maneuver, 3) Heart rate response to standing *(30:15)*. *Results:* We used the statistical analysis of 95% Normative Values for normal values. Next table shows the range of normal values.

	N_1	N_2	N_3	N_4
E/I index	1.28–1.76	1.22–1.59	1.14–1.51	1.09–1.35
MCR	47.5–163.7	38–119	22.5–97.5	15–44.2
SD	66–187	53.4–177.6	38–126	20.5–72.5
VALSALVA	1.28–2.4	1.31–2.7	1.28–2.23	1.20–1.55
Index 30:15	1.17–1.78	1.13–1.87	1.15–1.63	1.06–1.29

Next table shows the mean normal values ± sd. * = $p < 0.05$ versus the rest.

	N_1	N_2	N_3	N_4
E/I index	1.51 ± 1.13	1.40 ± 1.12*	1.33 ± 1.1*	1.19 ± 0.07*
MCR	93.4 ± 38	74.9 ± 23.5*	60.1 ± 25.8*	27.4 ± 8.9*
SD	113 ± 34.2	103.9 ± 39.9	72.6 ± 23.5*	35.6 ± 13.9*
VALSALVA	1.85 ± 0.29	1.73 ± 0.35*	1.65 ± 0.29*	1.36 ± 0.1*
Index 30:15	1.4 ± 0.16	1.39 ± 0.23	1.25 ± 0.14*	1.13 ± 0.06*

Conclusions: There is significant difference of normal value of 30: 15 index in comparison to those from publications for other populations. The other indices are similar with those reported in other populations. All indices decreased with the progression of age.

P25) Altered autonomic nervous system activity in elderly patients with dysautonomic syncope

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Introduction. Dysautonomic syncope (DS) is defined as a gradual decline in blood pressure without any change in heart rate which leads to loss of consciousness. This particular pattern of neurocardiogenic syncope seems to be more frequent in elderly patients with unexplained fainting. The aim of the study was to assess the differences in sympatho-vagal balance in elderly patients with and without DS.

Materials and methods. One-hundred and four patient had a positive response during HUTT (10 minutes of resting before undergoing a 20 minutes tilt at an angle of 60 degrees; continuous electrocardiographic and pressure recording were obtained for each patient): 78 patients had a vasovagal reaction (VS), while 26 developed a DS. The power spectral density of the baseline and tilt recordings were computed by an autoregressive algorithm; autonomic nervous system function was evaluated from two spectral components: high-frequency (HF, 0.16–0.40 Hz), and low-frequency (LF, 0.04–0.15 Hz). HF power is thought to arise from parasympathetic activity, LF from combined parasympathetic and sympathetic activity. The LF/HF ratio reflects sympathetic activity. A complete clinical and pharmacological history was collected for each subject.

Results. Values are expressed as mean+standard deviation of normalized units (NU). Patients with DS showed higher values of LF at rest (64.9 ± 7.7 vs. 57.5 ± 12.8 UN, $p = 0.037$), but a lower sympathetic activation during tilt with respect to patients who experienced VS (68.3 ± 12.2 vs. 80.9 ± 8.5, $p = 0.016$). As consequence, in DS group, LF/HF ratio was significantly higher than in patients with VS at rest, but this ratio didn't change during the upright position. Linear regression analysis showed that age > 80 is able to explain the 85% of variance, together with a number of drugs > 4 and a high degree of comorbidity.

Conclusions. In this study patients with DS showed a different pattern of sympathetic activation with respect to VS group: according to the multivariate analysis results, age itself is related to altered sympathetic response, but a high number of drugs and a poor clinical picture are responsible of a blunted autonomic response to the upright position.

P26) Changes in late potentials after b-blockade in myocardial infarction

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Purpose: "Late potentials" (LP) are detected by signal-average ECG, a nonivasive and easy test. LP are reflecting the autonomic activity of the patient's nervous system and play a significant role in detecting the patients with higher risk for dangerous cardiac arrhythmias after an acute myocardial infarction (AMI). The aim of the study was to evaluate the changes of LP after the administration of b-blockers in patients with AMI.

Methods: We considered 15 patients (12 men, 3 women, age 65.3 ± 11.5 years) with AMI in whom LP were measured in the 1st and in the 8th day of the AMI. All patients received b-blockers from the 1st day.

Results: Total filtered QRS duration changed from 112.3 ± 12.1 msec to 102.1 ± 7.2 msec ($p = 0.009$). RMS (root mean square voltage of the terminal 40 milliseconds) changed from 21.6 ± 10.1 μV to 32.3 ± 16.5 μV ($p = 0.04$). LAS [low amplitude (< 40 μV) signal duration] changed from 46.3 ± 14.8 msec to 35.4 ± 9.8 msec ($p = 0.024$).

Conclusions: The administration of b-blockers improves, by controlling adrenergic activity, all components of signal averaged ECG. This fact verifies the protective role of b-blockers after an AMI.

P27) Nictemeral changes of arterial blood pressure in the acute phase of ischemic stroke

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Purpose: Although changes in Arterial Blood Pressure (ABP) during stroke are well known, controversial data are reported when the acute phase of ischemic stroke and its different subtypes are considered. Aim of the study was to describe the changes of ABP in patients observed within 6 hours from the stroke onset.

Materials: 59 ischemic stroke patients, 38 previously hypertensive, were admitted to the study. Following TOAST criteria they were subdivided into atherothrombotic (19), cardioembolic (10) and lacunar (30).

Methods: a 24 hours systolic (SBP) and diastolic (DBP) blood pressure monitoring were performed at the admission (B) and after 7 days (C). The data series were treated through a statistical and chronobiological (Cosinor analysis) approach.

Results: in the whole population the 24 hrs ABP averages were significantly higher at B than at C ($p < 0.0001$) with lost of nictemeral changes. In B HT patients showed higher SBP values when compared to NH subjects ($p < 0.0001$). Both HT and NT groups were characterized by higher SBP and DBP values during day-time (06:00–22:00) then night-time (22:00–06:00) either at B or at C monitoring. A significant circadian rhythm of SBP was detected in the 66% of NT and 50% of HT at B and in the 33% and 47% respectively at C. The highest BP values were recorded in atherothrombotic and lacunar sub-

types which also exhibited significant nictemerali changes. Cardioembolic strokes was characterized by the lost of day-night variations and by higher BP values at 7th day.

Discussion: Our data showed that ABP profile during the acute phase of ischemic stroke depends on the type of stroke and on a previously history of hypertension. HT subjects as well as atherothrombotic and lacunar strokes are characterized by higher ABP values during the acute phase while a lack of circadian BP modification is detected only in cardioembolic strokes.

P28) Early identification of subjects with poor orthostatic tolerance

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An easy and low-cost method for identification of subjects prone to orthostatic vasovagal syncope would be of clinical benefit.

An orthostatic test with 60 deg head-up-tilt, and progressive lower-body-negative-pressure was performed on 79 patients with histories of unexplained syncope and 26 control subjects. Test was stopped at the onset of presyncope and time to presyncope was taken as a measure of orthostatic tolerance. Supine time series of R-R interval (ECG) and systolic pressure (Finapres) were recorded before the beginning of the test. The power of the high (respiratory) and low (LF ~ 0.1 Hz) frequency oscillations were quantified by spectral analysis. The LF central frequency (LF_freq), phase shift, and the transfer function gain between RR interval and systolic pressure fluctuations were provided by cross-spectral analysis, and measured at the point of maximal coherence.

According to reference values, 38 patients (PT) and 11 controls (CPT) were classified as having poor tolerance, whilst 41patients (NT) and 15 controls (CNT) displayed normal tolerance. Patients and controls with poor tolerance showed altered mechanisms of the LF oscillations. Particularly, the LF_freq in NT and in CNT was on average above 0.1 Hz and it was significantly higher than that in PT and CPT, who displayed a LF_freq around 0.09 Hz. Using our test of orthostatic tolerance as comparison, the LF_freq in supine allows the classification of subjects with poor or normal tolerance with 80 % sensitivity and 82 % specificity. Noteworthy, LF_freq is significant linearly correlated to the time of presyncope.

Conclusion – These results suggest that LF_freq in supine may provide a useful index in the diagnosis of orthostatic intolerance.

P29) Changes in sympathetic vasomotor responses with head-down bed rest

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Background and objectives: Cardiovascular deconditioning observed after spaceflights is characterized by orthostatic intolerance and decreased exercise capacity. Head-down bed rest (–6°) (HDBR) is a model commonly used to study the effects of microgravity. Inadequate cardiovascular autonomic regulation is one of the mechanisms involved in orthostatic intolerance but characterization of sympathetic changes is still poorly known. One of the objectives of this study was to assess sympathetic vasomotor responses during a 4 day HDBR.

Methods: Eight male healthy volunteers (mean age = 30.8 y) participated in the study. Blood pressure (BP) (Finapres) was recorded: during a 5 min cold pressor test (used to assess sympathetic vasomotor response) and before and one hour after administration of midodrine (5 mg) (a drug acting on vascular alpha receptors used in orthostatic hypotension treatment). These two tests were performed before HDBR (D´-1) and at the 4th day of HDBR (D4).

Results: Changes (in %) in systolic (S) and diastolic (D) BP during the two tests were calculated. BP variability was also analysed by spectral analysis (5 min period recordings). We looked at the power in Low Frequencies (LF) (0.04 to 0.15 Hz). Resting SBP and DBP did not change significantly at D4. Changes (%) in SBP and DBP tended to be lower at D4 during the cold pressor test (DBP: D-1: 21 %/D4: 15 %) (NS). Power in LF did not differ with HDBR at rest, during the cold pressor test and after midodrine administration. However changes in LF (%) after midodrine tended to be lower at D4 (mean (± SE): D-1: 6.3 % (± 10) – D4: 27 % (±14)) (NS).

Conclusion: These results suggest a reduced vasomotor response with HDBR in accordance with the reduced orthostatic tolerance, but have to be confirmed on a larger population.

Poster Session 3: Friday, May 17, 2002, 17.00–18.00

P30) The Valsalva maneuver and left ventricle diastolic dysfunction by diabetics

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*Introduction:*Valsalva maneuver is very known test in diagnosis of vagal denervation by diabetics, but also this test is very useful in diagnosis of cardiovascular dysfunction.

The aim: of the study was to establish significance of Valsalva maneuver in diagnosis of vagal denervation and correlation of test results with left ventricle dysfunction,arrhythmias and ischaemia by diabetics.

Methodology: 75 (37\M, 38\F) diabetics are being examined and divided into 3 groups in dependence of results:

1. Diabetics with negative test (n = 26, 17\M, 9\F)
2. Diabetics with borderline test (n = 23, 9\M, 14\F)
3. Diabetics with positive test (n = 26, 11\M, 15\F)

All diabetics were underwent to cardiovascular reflex tests (according to Ewing): Valsalva maneuver, deep breathing, 30\15 ratio test (for vagus), orthostatic hypotension test, hand grip test (for sympathicus).The most patients had 24 h Holter EKG Monitoring (with parameters: ischemia-ST depression > 1mm, disorder of rhythm: Lown > II, Lown < II) and echocardiograhy examination (systolic dysfunction-EF < 40 %, diastolic dysfunction-A > E, MMOD parameters).

Results: Diabetics with complete autonomic sympathetic and vagal denervation had positive test in 15 (57,69 %) cases, borderline in 12 (51,17 %) and negative in 4 (15,38 %) patients. p < 0,01. Diabetics with vagal denervation had positive test in 26 (100 %) p., borderline in 15 (65,21 %), negative in 4 (15,38 %) patients. p < 0,01Test of 30:15 ratio was positive in 18 (69,23 %) p.IIIG, 17 (73,91 %) p.IIG, 7 (26,92 %) p.IG. p < 0,01 Deep breathing test was positive in 20 (76,92 %) p.IIIG, 5 (21,73 %) p.IIG, 4 (15,38 %) p. IG. p < 0,01. Disorder of systolic function had 9 (39,13 %) p. with positive test, 3 (13,63 %) borderline and 6 (30 %) p. with negative test. p > 0,05 Disorder of diastolic function of left ventricle had 16 (69,56 %) p.IIIG, 10 (45,45 %) p.IIG and 8 (40 %) p.IG. p < 0,05 Disturbance of rhythm had 9 (47,36 %) d.IIIG, 8 (47,05 %) d.IIG, 5 (33,33 %) d.IG. p > 0,05 Ischaemia was present in 8 (40 %) p. with positive test, 8 (50 %) p. with borderline and by 3 (20 %) p. with negative test. p > 0,05.

Conclusions: All patients with vagal denervation had positive Valsalva maneuver and about 60 % patients with complete denerva-

tion.There is only statistical significance in correlation of positive Valsalva maneuver test with disorder of diastolic function.

P31) Effects of cisapride on gastroparesis in type 2 diabetics

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Aim: Investigation of the effects of cisapride on gastric emtpying in diabetic patients

Methods: Fifteen patients with type 2 diabetes mellitus were studied. All the subjects werte documented to have autonomic neuropathy and delayed gastric eptying. Autonomic neuropathy was assessed by standar cardiovascular reflex tests.

The measurement of gastric emptying was made by double isotope tests before and 12 weeks after of 40 mg/day ciapride administration. Symptoms related to gastric function were rated by the patients on a 3-point scale before and after treatment.

Results: After administration of cisapride for 12 weeks the gastric emptying of both solids and liquids was faster ($P < 0.01$, $P < 0.02$, respectively), and there were reported improvements in symptoms ($P < 0.001$).

Conglusions: These findings indicate that cisapride improves gastric emptying in type 2 diabetics with gastroparesis and is associated with a significant reduction in symptoms.

P32) The cardiovascular reflex tests in cardiovascular risk stratification by diabetics

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Introduction: Cardiovascular reflex tests are very useful in diagnosis of diabetic vagal denervation but also these tests are used in cardiovascular examination and risk stratification regarding to the fact that hyperactivity of sympathicus is leading factor in pathogenesis of sudden heart death.*The aim:* of the study was to establish significance of Valsalva maneuver, deep breathing test and 30\15 ratio test in diagnosis of vagal denervation and cardiovascular dysfunction by diabetics. *Methodology:* 75 (37\M, 38\F) diabetics are being examined and divided into 3 groups in dependence of results of tests according to Ewing: positive, borderline and negative. All diabetics were underwent to cardiovascular reflex tests (according to Ewing): Valsalva maneuver, deep breathing, 30\15 ratio test. The most patients had 24 h Holter ECG Monitoring (with parameters: ischemia-ST depression > 1mm, disorder of rhythm: Lown > II, Lown < II) and echocardiograhy examination (systolic dysfunction-EF < 40 %, diastolic dysfunction-A > E, MMOD parameters). *Results:* Diabetics with complete autonomic sympathetic and vagal denervation had positive Valsalva maneuver test in 15 (57,69 %) cases, deep breathing test in 22 (68,75 %) cases and 30:15 ratio test in 27 (57,44 %) cases. $p < 0,01$. Diabetics with vagal denervation had positive Valsalva maneuver in 26 (100 %) cases, 30:15 ratio test in 37 (78,72 %) cases and deep breathing test in 32 (100 %) cases. $P < 0,01$. Disorder of systolic function had 10 (35,71 %) p. with positive deep breathing test, 9 (47,36 %) borderline and 3 (11,53 %) p. with negative test. $p < 0,05$. Dilatation of left ventricle had 12 (42,85 %) p. with positive deep breathing test, 6 (31,57 %), borderline and 3 (11,53 %) p. with negative test. $p < 0,05$. Ischaemia with arrhythmias was present in 8 (38,09 %) p. with positive deep breathing test, 8 (66,66 %) with borderline and 3 (18,75 %) p. with negative test. $p < 0,05$. Ischaemia with disorder of rhythm was present in 14 (51,85 %) p. with positive 30:15 test, 4 (40 %) p. with borderline and by 1 (8,33 %) p. with negative test. $p < 0.05$.*Conclusions:* All patients with vagal denervation had positive Valsalva maneuver and deep breathing tests. Diabetics with complete autonomic neuropathy had positive deep breathing test in about 70 % cases, Valsalva maneuver and 30:15 ratio tests in about 60 % cases. Deep breathing test and 30:15 ratio test are more positive in patients with ischaemia and arrhythmias, and deep breathing test by patients with systolic dysfunction.

P33) Fractal analysis of heart rate dynamics in patients with diabetic autonomic neuropathy

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Background and Purpose: Different heartbeat power spectral densities are associated with various pathological conditions, such as diabetic autonomic neuropathy (DAN) and myocardial infarctions. Previous studies focus, for the most part, on the relative power in various spectral peaks. In this study, we examine the change of fractal structure of heart rate variability (HRV) between normal and DAN and therefore may provide a more general way of determining the degree of health and autonomic neuropathy. *Methods*: We studied 29 NIDDM and 12 age-matched controls (NL, aged = 57.5 ± 8.3yrs). All underwent a battery of cardiovascular tests (5 sets of tests). Patients were separated into two groups according to different severity of DAN with modified composite autonomic scores (MCAS): DAN1 with MCAS = 3 to 4 (n = 16) and DAN2 (severe severity) with MCAS ≥ 7 (n = 13). A time domain interval of HRV (RRIV) and power spectrum analysis of HRV in three bands (VLF, 0.015–0.07 Hz; LF, 0.07–0.15 Hz and HF, 0.15–0.40 Hz) and LF/HF were analyzed. The fractal analysis of HR was assessed during the 1-h recording in all subjects. We take several analyses to calculate the indexes based on interval and count measures. Interval measure consists of interval-based periodogram (IBP) and count measures consist of variance-time-curve (VTC) and Fano factor (FF). *Results*: RRIV (NL = 53 ms) was decreased significantly in DAN (DAN1 = 29 ms; DAN2 = 8 ms). The spectral power of HR in the LF and HF bands were significantly lower in diabetic patients than in healthy subjects but LF/HF remained unchanged. IBP (NL = 1.17 + 0.20) increased in DAN1 (1.36 + 0.18) and DAN2 (1.60 + 0.30) significantly. The VTC was not changed significantly between NL and DAN1 but was much decreased in DAN2 (1.61 + 0.15 Vs 1.78+0.14). FF values (NL = 0.80+0.07) were lower in all patients but did not reach significant level between DAN1 (= 0.87 + 0.05) and DAN2 (= 0.90 + 0.05). *Conclusion*: The major findings of the study are that HRV analysis is able to assess the impairment of the autonomic nervous system for diabetic neuropathy and the fractal analysis of HR was correlated with the MCAS. Therefore, both the standard deviation and the fractal dynamics of HR, contain information about the degree of impairment of the autonomic nervous system.

P34) RR and QT interval variability in patients with Parkinson's disease

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Background: Recently partial impairment and inhomogenity of cardiac sympathetic innervation has been described in patients with

Parkinson's disease. Cardiac sympathetic denervation may lead to repolarization abnormalities, which may be reflected in altered temporal QT variability.

Subjects: 20 patients with Parkinson's disease and proven autonomic dysfunction and 20 sex and age matched control subjects were studied.

Methods: One-lead ECG recordings were done in subjects resting supine for 5 minutes under standardised conditions and recordings were used for off line analysis.

The modified method introduced by Berger et al. was used in analysis of QT variability. Time series of QT and RR interval were constructed for each recording and power spectral analysis of QT and RR interval variability was performed (fast Fourier analysis). Integrals over low and high frequency bands (LFB and HFB) of spectra and sympthovagal coefficient (LFB/HFB) were calculated. Linear regression between QT and RR interval series was performed for each individual. Slope of regression line was used as a measure of QT-RR interval dependence.

Results: Both patients and controls had very low spectral power of QT variability, which did not differ between the groups. Patients had lower QT sympthovagal coefficient ($p < 0{,}005$), while spectral power of LFB and HFB did not differ from controls. Patients had also lower integrals of RR variability over LFB and HFB ($p < 0{,}001$), while RR sympathovagal coefficient did not differ from controls. Patients had significantly steeper slope of QT-RR interval regression line ($p < 0{,}02$).

Discussion: Patients with Parkinson's disease and autonomic dysfunction have altered myocardial repolarization. While dependence of QT interval on RR interval seems to remain preserved, direct autonomic influences on myocardium might be altered, which might be consequence of cardiac sympathetic denervation.

P35) Circadian Heart Rate Variability In Parkinson's Disease

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Purpose: Parkinson's disease is known to affect the reflectory cardiovascular autonomic control systems manifesting itself as abnormal blood pressure and heart rate (HR) responses. The present knowledge concerning the long-term characteristics of HR and HR variability, e. g. circadian regulation, is limited. The present study was designed to evaluate the effects of Parkinson's disease on the circadian fluctuation of HR variability.

Subjects: 44 untreated de novo patients with Parkinson's disease (18 men, 26 women, mean age 63 years) and 43 randomly selected healthy control subjects (14 men, 29 women, mean age 60 years) were included in the study.

Methods: 24-hour ambulatory ECG recording was performed in all the subjects. The circadian fluctuation of time domain (SDNN), frequency domain (low-frequency power, LF; high-frequency power, HF), two-dimensional Poincaré vector analysis (SD_1, SD_2), and some non-linear measures (fractal correlation parameters and approximate entropy) of HR variability were measured. The parameters were analysed in the blocks of 3600 seconds, and the results were presented separately for the night (from midnight to 6 AM) and for the daytime (from 9 AM to 9 PM).

Results: At night the spectral components LF (370 ms^2 vs. 785 ms^2, $p < 0.05$) and HF (169 vs. 348, $p < 0.05$) and the Poincaré value SD_1 (17 vs. 24, $p < 0.05$) that quantifies the short term beat-to-beat variability, were lower in the parkinsonian patients than in the controls. During the daytime only the Poincaré value SD_1 (14 vs. 17, $p < 0.05$) was suppressed. No differences between the two groups were found in the non-linear dynamic components of HR variability. The night-to-day-ratios of the HR variability measures did not differ significantly between the patients and the controls.

Conclusions: The results indicate that the long-term parasympathetic cardiovascular regulation is already affected by the pathological process of the Parkinson's disease in untreated de novo patients. The parasympathetic cardiac control is suppressed all day, but the dysfunctions seems to be more pronounced at night.

P36) Autonomic dysfunction in early stages of Parkinson's disease

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Aim: Although early severe autonomic involvement should alert the clinician for diagnosis other than P. D., autonomic disturbance is common in P. D. most commonly in late stages.

The purpose of this study is to investigate the prevalence of autonomic disturbances in early stages of P. D.

Subjects – Methods: Thirty patients (15M and 15F) mean age 60 ± 9 clinically diagnosed with P. D., Hoehn-Yahr scale score ≤ 2 and mean disease duration 4 ± 1 years were studied for autonomic dysfunction in the early stages of their disease. Exclusion criteria were those that Parkinson's Disease Society Brain Bank guidelines include among the elements necessary to reach correct diagnosis.

Results: A significant percentage of patients studied, 73 % (22 patients) complained with at least one Autonomic nervous system (A. N. S.) symptom.

	Orthostatic Hypotension	Seborrhea	Erectile Dysfunction	Urinary Bladder Problems	Gastrointestinal Problems (G. I.)
Patients	2	11	7	6	18
%	9 %	50 %	47 %	27 %	81 %

Among those who reported G. I. problems 13 patients (59 %) had constipation, 6 patients (27 %) swallowing difficulties, but not severe dysphagia and 5 patients (23 %) increased salivation.

However, elderly patients are expected to develop relatively earlier urinary bladder problems and erectile dysfunction than do younger onset patients due to concurrent Urological problems.

Conclusion: Autonomic involvement is a relatively late feature of P. D. However, some "autonomic" problems such as constipation, seborrhea, erectile difficulties and less frequently impaired swallowing and salivation seem to be present at the early stages of the disease where others (i. e. orthostatic hypotension, severe dysphagia) are uncommon.

P37) Is blood pressure dysregulation causing arteriosclerosis in parkinsonian patients?

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Introduction: Ultrasonographic measurement of intima-media-wall-thickness (IMI) of the common carotid artery (ACC) is used to describe extend of arteriosclerosis. As known, arterial hypertension is a risk factor for developing arteriosclerosis. In Parkinsonian patients (PD) with severe autonomic involvement blood pressure (RR) dysregulations can appear as orthostatic hypotension and/or loss of physiological nocturnal blood pressure decline or even nocturnal hypertension.

Aim of the following study was to detect, if these autonomic dysregulation with nocturnal blood pressure increase is a risk factor of developing end-organ damage or arteriosclerosis in PD.

Patients and methods: We examined 29 PD (15m, 14f), aged 67± years, UPDRS stage 49,3±25, in whom we applied discontinuous non-invasive 24-h RR-monitoring, ultrasonographic measurement of the IMI (determination in mm), tilt table testing and an autonomic questionaire. Patients with a diabetes mellitus were excluded.

Results: A physiological nocturnal blood pressure decrease was lost in 16 PDs, even 10 patients showed an nocturnal blood pressure increase compared to the day-time values. Mean nocturnal blood pressure was 132±19//76±13 mm Hg. IMI was 0,6± 0,25 mm (min 0.0,2; max 0.1,3 mm) and showed a significant correlation with nocturnal diastolic blood pressure increase and with a high score (= bad clinical results) in UPDRS.

Conclusion: PD with severe autonomic involvement such as nocturnal arterial hypertension are endangered to develop arteriosclerosis with subsequent cardio- or cerebrovascular endorgan damages. In predisposed PD risk reduction may be achieved by application of antihypertensive drugs in the evening.

P38) Autonomic function in scleroderma

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Introduction: Scleroderma is an autoimmune connective tissue disorder with characteristic skin lesions, Raynaud's phenomenon and visceral involvement.

As scleroderma lesions have a distribution similar to the pseudosyringomyelic pattern seen in some small fiber neuropathies, a possible pathogenetic role of the nervous system has been suggested.

Skin biopsies studies have shown increased density of NPY pos.-fibers, myelin disintegration and occasionally axon fragmentation.

Cardiac abnormalities, gastrointestinal dysmotility, abnormal SSR, altered vasomotor responses have been reported as proof of autonomic involvement in this disorder.

Aims: To evaluate the severity and distribution of autonomic dysfunction and to compare the distribution of autonomic and skin involvement.

Subjects and Methods: Ten scleroderma patients (8 women, 2 men) participated in the study. They underwent a complete neurologic examination, an autonomic reflex screen (including: tilt, deep-breathing, alsalva maneuver and QSART), orthostatic catecholamines measurements and thermoregulatory sweat test.

Results: Neurologic exam was normal in all except one subject who suffered from myopathy associated to scleroderma. Cardiovagal, adrenergic vasomotor, cardiosympathetic functions and catecholamine measurements were normal. Thermoregulatory sweat test was markedly abnormal in 7/10 subjects, with areas of anhidrosis involving proximal regions (forehead, chest, proximal limbs) and relative distal sparing, including the hands that were the most severely affected body segment in all of them (Fig. 1). These 7 patients reported itching in the involved areas to be a major symptom, while the remaining 3 did not.

Discussion: Hypo/anhidrosis in scleroderma has a different distribution to that of skin lesions, suggesting that is not simply due to excess of collagen disrupting sweat glands nor nerve function. Itching, which often precedes the appearance of new lesions, indicates C-fiber irritation or dysfunction. This suggests either a pathogenetic role of C-fibers in scleroderma or it may indicate they are targeted by same process that triggers the excess of collagen deposition.

P39) Autonomic nervous system function in mitochondrial disorders

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Aim of the study: Autonomic dysfunction including gastrointestinal dysmotility, cardiac arrhythmias, altered sweating and postural hypotension has been reported in mitochondrial disorders (MD). The aim of the study was to investigate autonomic function in MD.

Subjects: 13 subjects with mitochondrial encephalo-myopathies, aged 28–66 years, free from cardiac impairment were investigated.

Methods: A battery of cardiovascular reflex tests including beat to beat variability during quiet breathing and deep breathing, heart rate responses to standing and cutaneous cold stimulus, mental arithmetic and sustained handgrip was carried out in order to assess the parasympathetic and sympathetic function. Power spectral analysis (PSA) of heart rate variability was also performed.

Results: Six patients showed a definite sympathetic damage with two altered tests and three subjects had a borderline sympathetic dysfunction; 2/6 and 1/3 patients had a peripheral neuropathy associated. The parasympathetic pattern was impaired in only one patient. The mean value of beat to beat variation during deep breathing was significantly lower than in controls ($P < 0.007$). PSA of heart rate variability did not showed any relevant alteration in MD.

Conclusions: Our preliminary results demonstrate a sympathetic dysfunction in MD. Further studies to elucidate this kind of impairment are going on.

P40) Study of neurovegetative disorders in patients seeking medical advise in the emergency department of general hospital of Drama

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Purpose: of this study were the analysis of the type, the frequency and the distribution of neurovegetative disorders in patients registered in the emergency department (ED).

Material – Method: during the last four years (period 1997–2001) a total number of 497 individuals were examined in the ED of General Hospital of Drama, complaining for a part of the following symptoms: dizziness, diaphoresis, headache, flushing, numbness, and chest discomfort. These individuals were classified according to their personal medical history. For the statistical analysis used the method "Access 2000".

Results: the 212 (42,6 %) were males and 285 (57,3 %) females. According to their personal anamnesis 102 (20,5 %) were absolutely

healthy, 59 (11,8 %) suffered from chronic diseases (COPD – neoplastic disorders – degenerative CNS diseases), 52 (10,4 %) suffered from anxiety disorders, 126 (25,3 %) were hypertensive and 158 (31,7 %) suffered from coronary disease-multivascular disease.

Conclusions: the symptoms from the chest (tachycardia, palpitations, tingling, heartburn) occupied the majority of the incoming individuals. In patients with coronary disease was observed an increased frequency of symptoms from the chest (not correlated with the main disease), diaphoresis and numbness. Hypertensive patients mentioned mostly headache and numbness of the upper limbs. Symptoms from the chest, headache and dizziness were observed in the majority of healthy individuals whose family anamnesis revealed that 46 % of them lived together with persons who had neurovegetative disorders.

P41) Autonomic manifestations and status epilepticus in Panayiotopoulos syndrome: a case report

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Introduction: Panayiotopoulos syndrome (PS) [1] is a new idiopathic childhood epilepsy, recently recognised by the International League Against Epilepsy [2]. It can be best defined as "idiopathic susceptibility to early onset benign childhood seizures with EEG occipital or extra-occipital spikes", and manifests mainly with autonomic seizures [3]. Autonomic symptoms (mainly emesis) occur from onset in 80 % of seizures, with half of them lasting for more than 30 minutes to hours, thus amounting to autonomic status epilepticus. Emetic symptoms culminate to vomiting in 3/4 of the seizures. Other autonomic manifestations may occur either concurrently with emesis or later in the course of the seizure, and include pallor, mydriasis, cardio-respiratory, gastrointestinal and thermo-regulatory alterations, incontinence and hypersalivation. In at least 1/5 of the seizures the child becomes unresponsive, pale and flaccid (ictal syncope), before convulsions or in isolation. Behavioural disturbances, headache or various non-painful cephalic sensations are common particularly at onset. More conventional seizure manifestations often ensue: the child becomes confused or unresponsive, eyes may deviate to one side (60 %) or stare widely open. Half of the seizures end with hemi- or generalised convulsions. Remission in PS usually occurs within 2 years from onset. 1/3 of patients have a single seizure, and only 5 %–10 % suffer more than 10 seizures that sometimes may be very frequent but outcome is again favourable [3]. We present a child with PS and unusually frequent and prolonged autonomic seizures and autonomic status

Case presentation: A right handed boy of five years of age presented to us with a history of one and a half year of increasing frequency episodes associated with prodroma symptoms such as abdominal pain sickness, pallor, perspiration and irritability leading to a tonic seizure or a blackout and followed by headaches. The tonic seizures with rolling eyes and stiffness were witnessed on a number of occasions at school. Nocturnal episodes were also reported characterized by abrupt awaking with abdominal pain and feeling of nausea followed by a blackout or episodes of incontinence of urine with no convulsion. Acute episodes of lightheadedness pallor followed by a blackout resulting to head injuries were also reported. The episodes were as frequent as three to four per week.

His past medical history was unremarkable. His delivery and pregnancy were normal and his developmental milestones were normal. In the family history was reported that his grandfather was a migrainer. *Investigations*: He had two long EEG recordings, which were taken after a series of autonomic seizures and following a prolonged status epilepticus respectively. The first showed functional spikes over the right temporal and sylvian areas, and the second multifocal spikes with clear emphasis over the left wider temporal – parietal areas. Treatment was initiated with carbamazepine but with little effect.

Conclusion: The autonomic features of the Panayiotopoulos syndrome are well documented in the series of cases [4–6], however syncope attacks (ictal syncope) as a prominent clinical feature have not been included in the constellation of clinical presentations.

In the light of PS, the concept of "ictal syncope" in childhood clearly needs radical re-evaluation. It is currently hypothesised that in PS an inherent autonomic instability responds by generating autonomic seizures and status when cortical hyperexcitability triggers susceptible cortical-diencephalic-brainstem circuits. As the current epidemiological data seem to indicate, this hyperexcitable loop is mainly related to the early childhood and is short lived. Careful prospective and controlled studies of autonomic function will clarify the roles of the cortex and the brainstem in seizure generation and expression.

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P42) Study of afferent sensory fibers Ia in individuals of reduced height with diabetic autonomic neuropathy

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Aim: In this study we examined the afferent sensory fibers originating from muscle spindles (Ia) in adult diabetic individuals with assessed autonomic dysfunction which did not have any sign or neurophysiological findings of peripheral neuropathy and had a body height below average.

Material and methods: Bilateral H-Reflex monitoring from the soleus muscle and calculation of the H "Index" = 2* [height(cm)/ΔH-M(msec)]^2 proposed for latency evaluation of the H-Reflex in individuals of extreme stature by Guihéneuc and Ginet, were carried out in fifteen (15) adult individuals with attested autonomic dysfunction due to type 2 diabetes mellitus. They all were free of other known pathological affections all having a reduced body height (< 160 cm). Neurophysiological measurements were performed in all of them to exclude any individuals having a peripheral neuropathy concerning fibers of cerebrospinal origin.The same measurements were performed in 15 healthy controls also, with reduced body height.

Results: In 11 (73 %) individuals of the diabetic group H Index val-

ues were bilaterally or unilaterally outside normal limits (102.3 ± 7.16) although in all of them H-Reflex latency was within the range of normal limits (~30 msec) as well as its other parameters. In all these individuals neurophysiological measurements (conduction velocities and EMG) revealed no peripheral neuropathy. In the control group only 3 individuals (20 %) had an H Index unilaterally or bilaterally outside normal limits.

Conclusion: In diabetic individuals of reduced height H-Index value can be found outside normal limits, in comparison to the same value calculated in healthy controls of the same stature (3.65/1). This can possibly be revealing of a discrete impact on afferent sensory fibers of type Ia 'apart the rest assessed dysfunction of autonomic fibers due to diabetes.

Poster Session 4: Saturday, May 18, 2002, 11.00–12.00

P43) The pressor response to water drinking in tetraplegic patients

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Background. Water drinking elicits a profound sympathetically-mediated pressor response in autonomic failure patients. *Patients and Methods.* To further elucidate the mechanism of the response, we assessed the acute effect of drinking water on supine blood pressure and heart rate in 13 tetraplegic patients (12 men, 39 ± 4 years, BMI 25 ± 1 kg/m^2) with traumatic high spinal cord injury (C2-C7). In these patients, sympathetic efferent neurons are disconnected from brainstem input. Heart rate and finger blood pressure were recorded continuously. Brachial blood pressure was measured every 5 minutes by an automated device. Baroreflex sensitivity was assessed by the sequence method. Patients were placed in the supine position with the upper body elevated by 15°. After 30 min of rest in a quiet environment patients ingested 500 ml of low sodium non-sparkling water and the following 60 min were monitored. *Results.* Blood pressure at baseline was 114 ± 5/67 ± 3 mmHg. Water drinking elicited a pressor response that was apparent within five minutes and reached a maximum of 125 ± 9/71 ± 4 mmHg after 35 minutes ($P < 0.05$ compared with baseline for both, systolic andd diastolic values). Heart rate decreased from 64 ± 2 bpm at baseline to 60 ± 2 bpm ($p < 0.001$). Baroreflex sensitivity increased from 18 ± 5 msec/mmHg at baseline to 23 ± 6 msec/mmHg at 30 min after water drinking ($p < 0.01$). *Conclusion.* Water drinking leads to sympathetic activation even if the direct connection between brain stem cardiovascular centers and spinal sympathetic neurons is interrupted. This observation suggests that water drinking activates postganglionic sympathetic neurons either directly or through a spinal reflex mechanism.

P44) Profile of autonomic evolution after traumatic paraplegia

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Purpose: Autonomic nervous system activity is blunted after traumatic paraplegia and patients present with bursts of hyperactivity of its sympathetic arm as commonly shown by clinical parameters. However, the profile of evolution through the following months after the initial trauma was never described. *Methods:* We assessed hear from 3 to 30 weeks rate variability (HRV) and spontaneous baroreflex sensibility (sBRS) in a 57 years old man after the initial trauma. *Results:* ANS indices went from 5.47 to 8.69 10–4 ms^2 (Total power, ns), from 0.56 to 1.88 10–4 ms^2 (HF, ns), from 3.09 to 1.35 (LF/HF, $p < 0.01$) from 16.4 to 13.4 ms/mmHg (sBRS, ns), and from 4 to 11 (sequences BRS, $p < 0.05$). HFnu increas from 23.3 to 51.8 ($p < 0.01$) and LFnu decrease from 70.2 to 41.8 ($p < 0.1$). The changes were almost linear over the time. *Conclusion:* Globally, after the trauma, the total spectral power is much less than normal values and its increase does not reach statistical significance through the 30-week evolution while the parasympathetic arm is statistically increased compared to the sympathetic arm. Such evaluations may help quantify the patients recovery after traumatic paraplegia.

P45) Sympathetic skin response is useful in localising the level of spinal cord lesions'

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The sympathetic skin response (SSR) is a neurophysiological parameter that can be used to assess the completeness of spinal cord transection.

We investigated the SSR in hands and feet of patients with spinal lesions. Forty two patients (17 female, 25 male) were included, aged 23 to 88 years (mean = 62, SD = 17). The spinal cord lesions included neoplasm, syringomyelia, myelitis and spinal infarction. Thoracic or cervical lesions above T10 occasionally lead to abnormal hand SSR (71 % vs. 22 %; $p = 0.02$). Lower spinal cord lesions below T7 was rarely associated with abnormal hand SSR (27 % vs. 73 %, $p = 0.02$) For spinal lesions above L2 the SSR findings were most consistent with the sites of pathology with a sensitivity of 78 % and a specificity of 80 %. These findings are compatible with the known anatomy of the sympathetic nervous system. Further electrophysiological findings with clinical examples will be presented.

P46) The role of C-fibers on cutaneous vasodilatation by local warming

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Introduction: Local and neurogenic mechanisms control cutaneous blood flow (CBF). The sympathetic nerves mediate vasodilatation during whole body warming by cholinergic co-transmission. Instead, endothelial local factors for mild temperatures and unmyelinated C-fibers for high (noxious) temperatures mediate vasodilatation by local warming, without clear-cut between these two mechanisms.

Purpose: to evaluate the role of C-fibers on CBF regulation during local warming in different regions (hairy and glabrous skin).

Materials: CBF was assessed by Laser Doppler Flowmetry (LDF). A thermostated probe was used to record and warm the skin simultaneously.

Methods: The percent increases of CBF were evaluated in 20 subjects after local warming (35°–40°–44°C) in two different sites (fingertip of index and volar surface of forearm) to test the region that better showed vasodilatation. In a second step, the skin of forearm was treated by local topic anesthetic (8 subjects) and by capsaicin for 3 weeks (3 subjects) to obtain C-fibers transitory denervation. CBF percent modifications were assessed after progressive local warming (35°–38°–41°–44°C and 35°–44°C for 5 and 10 min. for each step). The

latency to reach the 50 % of maximal flow was also calculated (L50 %).

Results: there was a correlation between CBF increase and the degrees of local warming, better expressed in hairy skin (forearm). In the anesthetized forearm a significant CBF increase was observed only at 44°C for short time warming, while for longer times the same trend was observed also at 41°C. The values of L50 % were always increased in the anesthetized skin. The same profile was detected in the capsaicin treated areas.

Conclusions: hairy skin is the best region to study vasodilatation. In human, heat-induced vasodilatation is regulated by unmyelinated C-fibers, already at 41°C. The study of CBF during local warming has valuable clinical application in detecting unmyelinated C-fibers function.

P47) Exaggerated vagal activity in patients with gastro-esophageal reflux disease

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Background and Aim: Lower esophageal sphincter motility is controlled by the autonomic nervous system. A prevailing sympathetic activity increases the tonic contraction of the esophageal sphincter, while an increase of the vagal modulation reduces it and promotes possible gastro-esophageal reflux. In the present study we tested the hypothesis that an abnormal autonomic profile consisting in an excessive vagal activity might characterize gastro-esophageal reflux disease (GERD).

Subjects: 9 patients with GERD (5 M; 4 F; age: 49 ± 15 years) and 7 Controls (C), age and gender matched.

Methods: In supine position, every subject underwent 15 minutes continuous recording of ECG, blood pressure (BP, Finapres), and respiratory activity.

Power spectrum analysis provided the normalized power (nu) of the high frequency (HF, ~0.25 Hz) and low frequency (LF, 0.1 Hz) oscillatory components of RR interval variability, markers of cardiac parasympathetic and sympathetic modulatory activity, respectively. The LF/HF ratio was used to assess the sympatho-vagal instantaneous relationship.

Results: Mean RR interval, arterial pressure and respiratory rate were similar in both groups. Patients with GERD showed LF_{RR} (35.7 ± 16.1 nu) and LF/HF (0.7 ± 0.4) values lower than the ones observed in C (LF_{RR} 72.7 ± 12.2 nu; LF/HF 5.0 ± 3.7). Conversely, HF_{RR}, marker of the cardiac parasympathetic modulation, was higher in patients (54.2 ± 13.7 nu) than in C (22.6 ± 13.6 nu).

Conclusions: Patients with GERD seem to be characterized by an abnormal vagal modulation of heart period that is likely to reflect an enhanced parasympathetic activity as compared to controls. We hypothesize that an increased parasympathetic modulation might promote functional alterations of the esophageal lower sphincter, thus facilitating gastro-esophageal reflux.

P48) Gastric emptying after hemisolid food in amyotrophic lateral sclerosis

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Purpose/Aim: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder, characterized by progressive loss of motor neurons and involvement of several non motor systems. Subclinical involvement of the autonomic system in ALS has been described. In this study we compare the gastric emptying time in ALS (with normal autonomic function test) and normal subjects (controls).

Patients/Methods: We studied 8 de novo (untreted) ALS patients and 8 sex and age matched healthy controls. All were of drugs. None of the patients were diabetics. Fasting patients were given the standard hemi-solid meal, and gastric emptying was monitored with a gamma camera positioned over the stomach, recording data for 2 hours.

Results: After food half time emptying was significantly delayed in patients ALS, as compared with controls (81.3 ± 4.9, 48.9 ± 1.1 minutes $p < 0.001$). ALS patients had prolonged gastric emptying compared with the control subjects (120.2 ± 5.7, 77.7 ± 4.7minutes $p < 0.001$.

Conclusions: This demonstrates that delayed gastric emptying in ALS patients may be an early indicator of autonomic dysfunction.

P49) Abnormal hypoxic increase of blood pressure in ALS

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Objective: In ALS patients, sudden fatal cardiovascular dysfunction has been reported. Even in early stage ALS patients, arterial blood pressure was elevated and baroreflex sensitivity was reduced. Since the chemoreflex interacts with the baroreflex, we assessed hypoxic and hypercapnic cardiovascular responses in ALS patients compared to controls. *Patients and methods*: 14 ALS patients (mean age 50.8 years, vital capacity > 60 %) and 15 controls (mean age 58.4 years) were studied. We continuously monitored heart rate and blood pressure during baseline (3′), selective hypercapnia (CO_2 > 55 mmHg) and, after 20 minutes rest, selective hypoxia (decrease of O_2 saturation > 10 %) using a closed rebreathing system. Mean heart rate and systolic blood pressure during 100 heart beats during baseline and the rebreathing periods were compared. *Results*: In ALS, the heart rate was significantly higher than in the controls during baseline, hypercapnia and hypoxia ($p < 0.05$). Systolic blood pressure during baseline and during hypercapnia did not differ. However, during hypoxia we found a significant increase of the systolic blood pressure in the ALS patients (mean 133 to 140mmHg, $p = 0.02$), but not in the controls (mean 135 to 134mmHg, n. s). When normalised for O_2 saturation changes, the response in the ALS patients was significantly higher than in the controls ($p = 0.008$). *Discussion and conclusion*: The higher heart rate again indicates sympathetic hyperactivity in ALS. The increase of the blood pressure during hypoxia in ALS patients is similar to findings in patients with obstructive sleep apnea, known to be related to cardiac arrhythmia. Early use of non-invasive positive pressure ventilation (NIPPV) might help to prevent possible fatal cardiovascular events in ALS patients.

P50) Cardiac neurotransmission imaging in ALS demonstrated by I-123 MIBG-SPECT

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Purpose: To assess the degree of cardiac sympathetic dysfunction in amyotrophic lateral sclerosis (ALS). Autonomic dysfunction is not considered to be a clinical feature of ALS. Nevertheless, subclinical autonomic involvement is reported in ALS patients.

Subjects/Methods: Decreased sympathetic innervation was evalu-

ated by myocardial scintigraphy using the non-metabolized norepinephrine analogue I-123-metaiodobenzylguanidine (MIBG) and single photon emission computed tomography (SPECT). MIBG accumulates in presynaptic vesicles of sympathetic neurons. Decreased MIBG-uptake indicates postganglionic sympathetic dysfunction. Ischemic lesions caused by coronary artery disease (CAD) reduce MIBG-uptake. Therefore, myocardial perfusion scintigraphy with Tc–99m-Sestamibi (MIBI) was carried out in addition to MIBG-SPECT in all patients. Twenty-five patients with the established diagnosis of early ALS (Jablecki ALS-score, median = 10.75, range 3–22.5) were included in the study. MIBG results were compared with data obtained from an age-correlated control group including 15 healthy subjects (MIBG uptake 2.16 ± 0.26). Two patients in whom CAD was demonstrated by MIBI-SPECT were excluded from the study. A follow-up study was performed in 12 of the 25 patients (follow-up periods ranging from 5 to 18 months, mean 10,5 months).

Results: MIBG scintigraphy demonstrated a significant decrease of cardiac sympathetic innervation ALS patients (1.90 ± 0.19; $p < 0.01$). Follow-up MIBG-SPECT revealed a slight, statistically not significant increase of cardiac sympathetic dysfunction over time (1.85 ± 0.21; $p \leq 0.18$).

Conclusion: MIBG-SPECT is a sensitive method to assess the impairment of sympathetic cardiac innervation. The present results demonstrate altered post-ganglionic cardiac sympathetic innervation in early stages of ALS.

P51) Autonomic function in chronic inflammatory demyelinating polyneuropathy

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A number of phenotypic patterns of chronic demyelinating polineuropathy (CIDP) have been identified, such as classic distal and proximal weakness (CIDP-I), predominantly distal weakness (DADS) and predominantly distal weakness with IgM monoclonal gammopathy (DADS-M). The presence of autonomic neuropathy in CIDP patients has already been assessed in a previous study (1), although associated conditions were not considered and diagnostic criteria for CIDP had not yet been established.

The aim of the present study was to investigate autonomic function in patients with different patterns of CIDP.

Sixteen patients (aged 27–72, 10 males) fulfilled the electrodiagnostic criteria for CIDP and were classified as 11 CIDP-I, 4 DADS-M and 1 DADS. In four of the patients, CIDP-I was superimposed on diabetic distal symmetric polyneuropathy. Autonomic function was assessed with a battery of standard cardiovascular tests (Deep Breathing, Lying to Standing, Valsalva Manoeuvre and Postural Blood Pressure). Patients with at least two abnormal results in the cardiovascular tests were considered affected by autonomic neuropathy.

Severe autonomic neuropathy with postural hypotension was diagnosed in 4 patients (25%), of whom 3 CIDP-I with diabetic polyneuropathy and 1 DADS. Diabetes was present in 75% of patients with autonomic neuropathy and in 8.3% of those without ($p = 0.046$). In patients with and without autonomic neuropathy, there was no difference in age (57.2 ± 4.7 vs 53.9 ± 14.1) and disease duration (39.5 ± 46.8 vs 93.7 ± 93.2 months).

In conclusion, autonomic neuropathy may be found in diabetic patients affected by CIDP, whilst it is infrequent in isolated CIDP even with a long-term clinical history. Further studies on a larger sample of patients would be required, and the effects of immunosuppressive therapy on autonomic function should be evaluated.

References

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P52) Paroxysmal central thermoregulatory failure: case report and literature review

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Aim. Body temperature (BT) regulation depends on the activity of central, autonomic and neuroendocrine systems with the hypothalamus as a critical site for the integration of thermoregulatory responses. The aim was 1) to describe three cases with paroxysmal sweating and hyper and/or hypothermia as striking presentation of abnormal circadian rhythm of body core temperature (BcT°); 2) to review cases from the literature to define the clinical and laboratory features of central thermorgulatory failure (TF).

Subjects. We describe 3 male patients with recurrent episodes of sweating, followed by hypothermia with clinically general weakness, mental slowness, chills and feeling cold. Intermittent hyperthermia was present in patients 1 and 2 who respective diagnose of neurosarcoidosis and Rubinstein-Taybi syndrome associated with a hypoplastic corpus callosum and overlap syndrome. In patient 3, additional clinical features and abnormal endocrine function were suggestive of hypopituitarism.

Methods. Systolic postural hypotension was found in case 3 ($\Delta = -30$ mmHg). The study of circadian rhythm of BcT°, by continuous monitoring of rectal temperature (rT°) was evaluated for 48 hours in cases 1 and 2 and for 24 hours in case 3.

Results. The recording of rT°displayed wide swings of over 2°C occurring throught the 24 hours. In cases 1 and 2, the rT°did not show the physiological nocturnal decrease but reached 38.5 °C in the early morning. The onset of sweating was immediately followed by a progressive fall in rT° (nadir: 33.7 °C, pt 1; 35.1 °C, pt 2; 32.8 °C, pt 3) which lasted several hours. Then, the rT° slowly returned to normal basal values in patient 3 (37.1 °C) and to higher values in the others (pt 1: 38.9 °C; pt 2, 38.5 °C). In patient 3, each episode was also associated with a sharp fall in blood pressure.

Conclusion Our cases developed central TF characterised by an abnormal shift of the hypothalamic thermoregulatory set-point with a delay in mechanisms for heat production or heat conservation, leading to hyperthermia and hypothermia. A selective hypothalamic lesion of different etiology may have caused the autonomic and neuroendocrine alteration responsible for TF. Diagnosis of TF should be considered in patients with abnormal sweating, especially if other autonomic or endocrine disorders are present. Clinical and laboratory evaluations are essential to recognize thermoregulatory disorders, to avoid the complications of severe hypo/hyperthermia and better define pathogenetic mechanisms.

P53) Cardiovascular autonomic nervous system function in primary amyloidosis

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Purpose: Primary amyloidosis is a rare disease with poor prognosis. Dysfunction of Autonomic Nervous System *(ANS)* usually exists. We report our findings from investigation of ANS impairment in patients with primary amyloidosis.

Patients-methods: We studied 5 patients (4 men, 1 woman) with mean age 61.8 years (range 54–65 years), who were hospitalized in our department during last 5 years. The clinical features of the patients were loss of weight, anorexia, fatigue, oedema of lower extremities, orthostatic hypotension and diarrhoea. All patients had monoclonal proteins ë or ê light chain increased and albuminuria (1.5–15 gr/24h). Diagnosis was established by tissue biopsy (kidney, liver, stomach, rectum). To assess ANS function, all patients underwent the following 4 standard cardiovascular reflex tests: 1) Heart rate variation during deep breathing [analyzed by Expiration/Inspiration index *(E/I index)*, Mean Circular Resultant *(MCR, vector analysis)*, Standard Deviation *(SD)*], 2) Valsalva maneuver *(Valsalva)*, 3) Heart rate response to standing *(30:15 index)* and 4) Blood pressure response to standing *(orthostatic hypotension)*. In 1988, a consensus statement of the American Diabetes Association and the American Academy of Neurology recommended the previous battery of tests.

Results: All patients had abnormal all the indices of cardiovascular reflex tests, indicating severe dysfunction of ANS. The mean values of the indices were the following: E/I index = 1.02, MCR = 8, SD = 12, Valsalva = 1.08, 30:15 index = 1.01, Orthostatic Hypotension = 40 mmHg. All patients underwent treatment with melphalan, colchicine and corticosteroids. Three of them did not response to treatment and died (pulmonary oedema 1, sudden cardiac death 2 due to malignant ventricular arrhythmias, but no myocardial infarction). One patient is in stable condition for 2.5 years. In the last patient, primary amyloidosis has been recently diagnosed and the effect of treatment has not yet been established.

Conclusions: ANS dysfunction is common and prominent in primary amyloidosis and it cares poor prognosis.

P54) A Novel Dysautonomia Related to the Benign Hypermobility Syndrome.

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Introduction: Symptoms related to the autonomic nervous system found to be frequent among patients with hypermobility syndrome (HMS). The aim of this study was to investigate the pathophysiology of the autonomic nervous system regulating the cardiovascular system in HMS patients.

Subjects and Methods: Forty nine HMS patients, who fulfilled the Brighton criteria, and 21 healthy controls, went through autonomic evaluation. Orthostatic test, cardiovascular vagal and sympathetic functions, catecholamines, and evaluations of adrenoreceptors responsiveness were compared between HMS patients and controls.

Results: Upright ΔHR and ΔSBP were 22 ± 2 vs 15 ± 2 bpm, and –8.5 ± 1.8 vs –1.2 ± 1.2 mmHg, p = 0.04 and p = 0.005 for patients and controls respectively. HMS patients presented different sympathetic and vagal control of the cardiovascular system. Valsalva ratio was significantly higher in HMS patients 1.7 ± 0.09 vs 1.31 ± 0.02, p = 0.002. Sympathetic indices showed a major drop and a higher increase systolic BP during hyperventilation and after cold pressor test in HMS patients as compared to controls: –11.5 ± 1.6 vs –5.5 ± 1.4 mmHg, p = 0.02 and 18.5 ± 2.5 vs 11 ± 3.5 mmHg, p = 0.06. Also, patients presented adrenoreceptor (AR) hyper-responsiveness, as assessed by ISO_{15} (a measure of β_1-AR sensitivity, the dose of isoproterenol required to increase HR by 15 bpm), 0.13 ± 0.03 vs 0.25 ± 0.05 μg (p = 0.04), and PHE_{15} (α_1-AR sensitivity, the dose of phenylephrine required to increase the systolic BP by 15 mmHg), 120 ± 11 vs 185 ± 27 μg (p = 0.03). Plasma norepinephrine concentrations were similar in both group.

Conclusions: The autonomic nervous system related symptoms of HMS patients have a pathophysiological basis, which suggest that dysautonomia is part of the syndrome such as syncope, POTS and mild orthostatic hypotension.

P55) Effect of static and dynamic LBNP on cerebral blood flow

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Cerebral autoregulation normally operates across a range of cerebral perfusion pressures to maintain cerebral blood flow almost constant. In this study, we examined whether there is a difference in the filtering of sympathetic-mediated and mechanically-induced BP oscillations by the cerebral circulation.

16 healthy subjects (mean age 27 ± 1.8 years) were studied in the supine position and then during static and oscillating (0.1 Hz) lower body negative pressure (LBNP), each applied at –40 mmHg. Autoregressive spectral analysis was used to obtain the powers of low frequency (LF, 0.04–0.15 Hz) oscillations of mean arterial pressure (MAP) and cerebral blood flow velocity (CBFV).

Static LBNP at –40 mmHg significantly increased the LF power of MAP from 1.01 ± 0.16 to 4.58 ± 1.06 $mmHg^2$ ($P < 0.05$) but the increase in the LF power of CBFV (from 2.05 ± 0.38 to 3.20 ± 1.19 cm/s^2) was not significant.

Oscillating 0.1 Hz LBNP at –40 mmHg significantly increased the LF power of MAP from 0.79 ± 0.21 to 3.30 ± 0.56 $mmHg^2$ ($P < 0.05$) and the LF power of CBFV from 1.60 ± 0.22 cm/s^2 to 5.24 ± 1.15 cm/s^2 ($P < 0.05$).

The LF power of MAP during oscillating LBNP did not differ significantly to that recorded during static LBNP. However, the LF power of CBFV was significantly greater during oscillating LBNP than during static LBNP at the same level ($P < 0.05$).

Mechanically-induced BP fluctuations by oscillating LBNP are transmitted onto the cerebral vessels. In contrast, increased sympathetic-mediated spontaneous LF-BP oscillations during static LBNP are not transferred onto the cerebral circulation, suggesting effects of the central autonomic network on cerebral autoregulation.

P56) Autonomic activity during stress test as a predictor for psychiatric illness

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Purpose: Many patients with atypical cardiac symptoms (usually called as autonomic symptoms) are referred to cardiology departments. Most of them undergo treadmill stress test (TST) in order to be differentiated from those with real cardiac problems. Many of these patients are found to suffer from mild psychiatric illness. The aim of the study was to evaluate whether the changes of heart rate during TST could predict such psychiatric illness.

Methods: We considered 18 patients – Group A – (6 men, 12 women, age 53.3 ± 12.8 years) with a diagnosed (after psychiatric review) mild psychiatric illness (anxiety neurosis 39 %, panic disorders 33 %, depression 17 %, simple phobia 11 %) and who presented with atypical cardiac symptoms. All patients underwent TST and the results were compared with those of 20 age-matched controls – Group B – who also underwent TST. All TSTs were negative for ischemia.

Results: Pre-test heart rate was 102.3 ± 16.4/min for Group A and 76.1 ± 13.2/min for group B (p = 0.000). Heart rate at the 5th minute of the TST was143.2 ± 13.6/min for Group A and 131.4 ± 10.3/min for group B (p = 0.004). At recovery, a significant delay in restoration of heart rate was noticed in group A since at the 5th minute of recovery heart rate was106.2 ± 8.2/min for Group A and 85.7 ± 12.3/min for group B (p = 0.000). Heart rate at peak exercise did not differ in the two groups [165.5 ± 6.2/min for Group A and 162.3 ± 9.2/min for group B (p = 0.22)].

Conclusions: A higher pre-test heart rate and a persisting high heart rate at recovery is may be due to greater adrenergic activity, may reflects to greater prevalence of anxiety and is may be a predictor of psychiatric illness among these patients. Such patients with atypical cardiac symptoms that are suspected to be caused by autonomic hyperactivity should be probably advised to undergo a psychiatric review.

P57) Fabry patients show impaired limb blood flow

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In Fabry disease, deficiency of α-galactosidase A induces glycolipid storage in small vessel walls. These deposits account for neuropathy, myocardial infarction, renal failure and stroke at early ages. To evaluate blood flow and vessel reagibility of Fabry patients noninvasively, we performed venous occlusion plethysmography and postischemic flow measurements in patients and healthy controls.

Fourteen Fabry patients (mean age 28.8 ± 9.1 yrs.) and 15 healthy controls (mean age 30.2 ± 8.4 yrs.) underwent venous occlusion plethysmography (Hokanson Inc.) by inflation of the arm cuff to 50 mmHg using sixteen repeated measurements. The blood flow was expressed as % volume change/minute during venous occlusion and was calculated as the average arterial influx of eight artifact-free measurements. Postischemic vasoreagibility was determined as the influx peak during the first venous occlusion following 3 min of ischemia induced by inflating the arm cuff above systolic blood pressure. Skin blood flow (SBF) was monitored at the index finger pulp before, during and after ischemia (Perimed™).

Baseline blood inflow during venous occlusion was lower in Fabry patients (5.6 ± 4.2 %/min) than in controls (6.1 ± 1.4 %/min; $p < 0.05$), as was postischemic hyperperfusion (14.9 ± 7.8 %/min vs. 16.9 ± 2.9 %/min; $p < 0.05$). Before ischemia, SBF did not differ between patients (312.3 ± 358.3 PU) and controls (217.5 ± 102.5 PU). During ischemia, SBF dropped to lower values in patients (0.1 ± 0.4 PU) than in controls (3.2 ± 0.9 PU; $p < 0.05$). SBF during hyperemia was significantly higher in patients (561.1 ± 315.2 PU) than in controls (266.1 ± 65.1 PU; $p < 0.05$).

Reduction of baseline influx and ischemia induced skin hypoperfusion indicate impaired forearm blood flow due to glycolipid deposits in blood vessels. Reduction of postischemic influx shows impaired vessel reagibility. The postischemic increase of SBF suggests increased sensitivity of superficial skin vessels towards ischemia. The discrepancy between reduced overall influx and increased SBF after ischemia might suggest different impairment at the level of arterioles and small skin vessels and requires further evaluation.