Neurological risk profile in organic erectile impotence

E Kunesch, K Reiners, V Müller-Mattheis, T Strohmeyer, R Ackermann, H-J Freund

Abstract

Thirty men who presented with erectile impotence to the urological department underwent a thorough urological, angiological, and neurological examination with complementary neurophysiological tests of somatosensory and sympathetic and parasympathetic function. Most had vascular and neurological abnormalities. Clinical findings and electrophysiological tests for autonomic dysfunction had the highest yield of abnormal results. Nerve conduction studies and pudendal nerve somatosensory evoked potentials were far less informative. The lack of correlation between vascular and general neurological abnormalities emphasises that patients must be screened for both vascular and neurological dysfunction to prevent unrewarding vascular operation in impotent men.

Introduction

Erectile impotence is defined as the persistent inability of the patient to obtain or maintain an erection suitable for vaginal penetration and the subsequent coital act.¹ Erectile impotence is commonly attributed to three main causes: vascular disease, neurological disturbances, and psychological factors. Erection requires a sufficient arterial blood supply of the corpora cavernosa arising from terminal branches of the internal pudendal artery² and intact arteriolar sphincter mechanisms, which either fill the corpora cavernosa or shunt blood into the veins. By inflow of arterial blood into the penile sinoids these get distended and compress the draining veins against the tunica albuginea. Thus venous outflow is reduced. In the cat, Semans and Langworthy³ were able to reproduce erection, emission, and ejaculation in a normal sequence by stimulating parasympathetic, sympathetic, and somatic nerve fibres supplying the male sexual organs. Erection is mediated by efferent parasympathetic nervi erigentes arising from the S2, S3, and S4 segments of the spinal cord. Afferent somatic fibres of the pudendal nerve (S2, S3, and S4 segments) may trigger erections on local stimulation. Stimulation of sympathetic nerves (D12, L1, and L2 segments) is required for emission of seminal fluid and later detumescence. For expulsion of seminal fluid from the urethra, however, stimulation of somatic and autonomic nerve fibres of the pudendal nerve is necessary. In the absence of local stimulation, erections after cerebral stimulation may

be initiated via sympathetic pathways.⁴ These findings indicate that normal male sexual function is critically dependent on the dynamic interplay of the parasympathetic, sympathetic, and somatic nervous system. Diagnostic urological evaluation of the erectile system has been considerably improved by the introduction of objective tests such as Doppler measurements of penile blood pressure and blood flow,^{5,6} pharmacodynamic cavernosography,^{7,8} pudendal arteriography,² and the nocturnal penile tumescence test.^{9,10}

Only during recent years have neurological test methods for the assessment of erectile nerve dysfunction become available, complementing clinical neurological investigation. These include the pudendal somatosensory evoked potentials^{11,12} and the electrically induced bulbocavernosus reflex¹³⁻¹⁵ to screen for the sensorimotor pathways and screening methods of autonomic dysfunction—sympathetic skin response,¹⁶ 30/15 test,¹⁷ and respiratory heart rate variation.^{18,19}

In our study 30 consecutive patients who had received a thorough urological investigation, including vascular function tests were investigated both clinically and by using an extended electrophysiological neurological test battery. We assessed the prevalence of autonomic neuropathy or other neurological disease and correlated these results to urovascular pathology.

Patients and methods

SUBJECTS AND CLINICAL INVESTIGATION

We studied 30 men aged 21–82 years (mean 45 years; interquartile ranges: 21–38, 39–46, 47–54, and 55–82 years) complaining of complete erectile impotence for 12 months to five years. All were referred outpatients from the urological department. Each patient had a thorough medical history taken including vegetative function and drug history. Physical examination included an assessment of neurological, urogenital, and vascular abnormalities. Neurological examination placed special emphasis on possible symptoms arising from dysfunction of the spinal cord, including anal and cremaster reflexes, and the peripheral sensorimotor and autonomic nervous system. Laboratory tests included blood cell count, blood glucose and lipids (cholesterol, triglycerids), liver and kidney function, and sex hormones. The table gives further details. The results in each category were tested for linear correlation with all other categories with Stat-View II statistical software (Abacus Concepts

Heinrich-Heine
Universität,
Moorenstraße 5
W-4000 Düsseldorf,
FRG
Neurology Clinic
E Kunesch
K Reiners
H-J Freund

Urology Clinic
V Müller-Mattheis
T Strohmeyer
R Ackermann

Correspondence to
Dr Kunesch

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Table Categories and tests evaluated in 30 men with erectile impotence

Category	Test items	Criteria for abnormal test result	Criteria for abnormal category
Neuropathic risk factors	Alcohol abuse	> 70g Ethyl-alcohol/day for > 6 months before examination	
	Diabetes Uraemia	Known for > 6 months Known for > 6 months	One or more out of three items abnormal
Sensorimotor neuropathy	Clinical examination	Depressed tendon reflexes, distal sensory loss, distal muscle wasting	
	Motor nerve conduction (tibial nerve)	Below mean (2SD) of 43 m/s (for 20 years) to 35 m/s (for 80 years) at 33°C	Two or more out of three items abnormal
	Sensory nerve conduction (sural nerve)	Below mean (2SD) of 48 m/s (for 20 years) to 45 m/s (for 80 years) at 35°C	
Autonomic dysfunction	Sympathetic skin response	Absent from foot (all patients with absent responses from hand also had no responses from foot) ¹⁶	
	Respiratory heart rate variation	Below age related normal range: ^{16,22} for example, for 30 years, 20/min; for 80 years, 5/min	Two or more out of three items abnormal
	30/15 Test	≤ 1.03 ¹⁷	
Pudendal SEP	Latency	Absent or latency above normal range (36 ms for 170 cm, 39 ms for 185 cm)	Considered abnormal only if peripheral nerve conduction studies were normal
Bulbocavernosus reflex	Latency	Absent or latency above 37.2 ms	Considered abnormal only if peripheral nerve conduction studies were normal
Vascular disease	Doppler ultrasound of penile blood flow		
	Penile cavernosogram		
	Arteriogram of pelvic arteries		One or more out of three tests abnormal
Vascular risk factors	Arterial hypertension		
	Nicotine abuse	> 10 Cigarettes/day for > 5 years	
	Diabetes mellitus		Two or more out of five items abnormal
	Elevated blood lipids		
	History of coronary heart disease		
Serum levels of sex hormones	Estradiol	> 80 pg/ml	
	Testosterone	< 2.7 ng/ml	
	FSH	< 1 or > 14 U/ml	One or more tests abnormal
	Prolactine	> 14.5 ng/ml	

Inc, Berkeley, CA, USA). All investigations were carried out with informed consent and according to the Declaration of Helsinki (1975).

ELECTROPHYSIOLOGICAL INVESTIGATIONS

The 30/15 test was carried out with a conventional ECG apparatus. All other tests were performed with a Medelec MS 20 Electrophysiological System (Mystro: Medelec, Woking, UK). If electrophysiological data were compared with normal data established in the literature, care was taken to adhere to the procedures as reported.

Nerve conduction studies—Investigation of nerve conduction velocities of the sural (antidromic) and tibial nerves was performed in the conventional way with bipolar surface electrodes. The filter band pass was 20 Hz–2 kHz for sensory nerve conduction measurements and 3 Hz–10 kHz for motor conduction measurements. The skin surface temperature from the dorsum of the foot was measured by means of a thermoelement. The normal values of nerve conduction velocities given by Ludin²⁰ were generally accepted and adjusted with respect to skin temperature (– 2 m/s for 1°C below the reference temperature indicated in the table).

Bulbocavernosus reflex (BCR)—The pudendal nerve was stimulated on the penis shaft by two surface ring electrodes with the anode placed distally at 80–150V (stimulus duration 100–500 µs) as described by Tackmann and Porst.²¹ The response was recorded by means of bipolar surface electrodes (Toennies) mid-

way between the scrotum and the anus. The anode was placed at the anterior superior iliac spine. The sweep speed was set to 10 ms/div and the filter band pass to 10 Hz–3 kHz: 32 sweeps were averaged. The latency was determined from the first negative deflection of the response (see figure 1). The response was considered to be abnormal if the onset latency was longer than 37.2 ms. Normal latencies are not consistently age dependent so no correction for age was necessary.

Pudendal SEP—Stimulation ring electrodes were placed at the shaft of the penis (anode distally) as described above. The somatosensory evoked potentials were recorded from the scalp with the active needle electrode (impedance 3Ω) placed subcutaneously 2 cm behind Cz. The reference needle electrode was inserted at Fz; 300 to 800 sweeps were averaged, and each test was repeated up to three times in order to assess the reproducibility of the evoked responses. The sweep speed was set to 10 ms/div and the filter band pass from 20 Hz–2 kHz. The latency of the response was measured from the P40 wave (figure 1) according to Haldeman *et al*^{11,12} and Tackmann and Porst.²¹ Response onset latencies longer than the body height dependent control limits given by Tackmann and Porst²¹ were considered abnormal.

Respiratory heart rate variation (HRV)—The method has been described in detail in a previous article.¹⁹ Briefly, the built-in single fibre EMG-software program of the Medelec MS 20 electrophysiological system was used to

record 50 RR intervals (ECG) during consecutive deep inspiration and expiration cycles (6/min). Conventional ECG plate electrodes were placed on the right foot and on the left or right arm and connected to the positive and negative input sockets of the MS 20 differential preamplifier. The sweep was triggered by the QRS complex, and the ECG activity was recorded with a gain of 200 or 500 mV/div, a filter band pass from 1-50 Hz, and a sweep duration of 1-2s depending on the heart rate so that QRS pairs consisting of the triggering and the subsequent QRS complex could be monitored on the same sweep. The variation of the time interval between consecutive QRS complexes was assessed for 50 QRS pairs. Variation was expressed as the difference between the frequencies calculated from the shortest and the longest RR interval found within an analysis period of approximately 45s. In our experience HRV is almost linearly age dependent to the same extent as described by Low *et al.*²² The table shows our lower normal limits for the extreme ages of our patients.

Sympathetic skin response (SSR)—The biphasic skin DC-potential shift in response to electrical shock stimuli was evaluated on the right hand and foot as described by Shahani *et al.*¹⁶ Toennies surface electrodes were attached to the volar and dorsal side of the hand and the plantar and dorsal side of the foot. The patient was instructed to relax in order to avoid artifact contamination by tonic muscle activation. Supramaximal electrical shock stimuli were applied randomly to the median or tibial nerve of the contralateral side. Care was taken to apply the next stimulus no earlier than 20s after the previous one in order to avoid habituation of the response. Sweep speed was set to 500 ms/div and amplitude gain to 100, 200, or 500 μ V/div as suitable. The filter band pass was set to 3 Hz–3 kHz. The response was considered to be present if clear biphasic responses could be obtained at latencies of 1–3s during several trials. If necessary, the foot was warmed up to skin surface temperatures above 28°C either by bathing the foot in warm water or by applying infrared light. The test was considered to be abnormal if responses were consistently absent.¹⁶

30/15 Test—Heart rate variation in response to orthostasis was assessed as described by Ewing *et al.*¹⁷ The patient lay supine and relaxed and was instructed to take an upright standing position as fast as possible. The RR interval between the 15th to 16th and between the 30th to 31st QRS complex after attaining the upright position was measured and the ratio (30th/31st divided by 15th/16th interval) was calculated. According to Ewing¹⁷ the normal ratio is above 1.03. There is a tendency for older patients to have lower values than younger ones, but in our experience even older healthy people retain a ratio above 1.03.

UROLOGICAL INVESTIGATION

This included a thorough clinical urological investigation, invasive angiography of the main

pelvic arteries, and cavernosography of penile veins as well as an assessment of the penile arterial blood flow by means of Doppler ultrasound techniques and of sex hormone serum levels.

Results

CLINICAL NEUROLOGICAL INVESTIGATION

The whole test battery was performed in all 30 patients. Two patients were normal in all tests but had major problems that made a psychological disease the most likely factor and they were excluded from further evaluation. Clinical neurological findings were abnormal in 15 of the 28 remaining patients. Most showed signs of sensorimotor as well as autonomic neuropathy. No patient had signs of a cerebral lesion or of pituitary or hypothalamic dysfunction. One patient had a history of a spine trauma without residual deficits, and the occurrence of impotence was temporally unrelated to the trauma.

TYPICAL RESULTS OF ELECTROPHYSIOLOGICAL INVESTIGATIONS

The upper panel of figure 1 shows the pattern of the bulbocavernosus reflex in three patients

Figure 1 Examples of normal, delayed, and absent responses for bulbocavernosus reflex measurements and pudendal SEP. For all cases two trials with 32 (bulbocavernosus reflex) and 300–500 averaged sweeps (pudendal SEP) are illustrated. Points at which latencies were measured indicated by arrows. Negative is up.

with erectile impotence. The response of patient 1 (two upper traces) was normal, that of patient 2 was delayed (traces 3 and 4), and in patient 3 no response was obtained (traces 5 and 6). Examples of pudendal SEP investigations are shown in the lower panel in figure 1. The pudendal SEP study of patient 1 (two upper traces) was normal, whereas in patient 3 no cortical response could be recorded (two lower traces). For the assessment of autonomic nerve function the 30/15-test, the HRV and the SSR were used. Examples are illustrated in figure 2. The upper two traces of both the upper and lower panel (patient 4) show normal SSRs recorded from the right hand and foot. Response latencies after the electrical stimulus were approximately 1.2–2 s. The lower traces (patient 5) show examples of absent responses. The responses from hand and foot remained absent in several trials. Examples of HRV recordings are illustrated in figure 3. Patient 4 had a normal HRV of 29/min (left panel), whereas the result of patient 5 (right panel) was abnormal (7/min).

INCIDENCE OF ABNORMAL FINDINGS

Clinical neurological findings, SSR in the foot, and the 30/15 test were often abnormal (16 out of 30 (53%), 16 (53%), 17 (57%)) whereas the pudendal SEP was abnormal only in three (figure 4). Only one out of eight patients with abnormal bulbocavernosus reflexes had no other pathological neurological findings or neuropathic risk factors. Urological examination showed that angiography was abnormal in 21 patients (angiography of pelvic arteries in eight, arterial penile blood flow in 20) and cavernosography in eight, but serum hormone levels were abnormal in only five (figure 4b). Polyneuropathy and vascular risk factors were found in half (figure 4c and d). Pathological

findings in neurological and urovascular categories were found in 19 patients. Seven patients were affected only urologically, and three only neurologically. The upper panel of figure 5 illustrates the distribution of normal and abnormal findings among our patients for clinical neurological examination, autonomic tests and nerve conduction velocity studies. Six out of 13 patients with more than one abnormal autonomic test result were normal on clinical examination. Eleven out of 13 patients had signs of both sympathetic and parasympathetic dysfunction. The coincidence of abnormal findings in both SSR and 30/15 test was high (figure 5, lower panel). Autonomic dysfunction was more often observed than sensorimotor neuropathy (13 v nine patients). None of the patients with sensorimotor neuropathy would have been missed even if nerve conduction studies had not been performed as in all these patients clinical neurological examination had already revealed abnormal findings. No significant correlations were found within the 95% confidence limits between the categories listed in the table. While most (24) patients were aged between 24 and 64 years only three out of 30 were 65 years or older. The number of pathological findings in all categories varied positively but not significantly ($p > 0.05$) with age.

Discussion

EXPERIMENTAL LIMITATIONS

There are some limits in the interpretation of our results. Firstly, our patients were referred from the urological outpatient department and may, owing to a preselection bias for urological problems, not be representative of the population of impotent men. Even in this urological selection of patients, however, a high incidence of urological and neurological abnormalities was found. The number of abnormal neurological findings would probably have been even higher in a sample of neurological patients—for example, multiple sclerosis is a common cause of erectile impotence. A structured psychological interview and more specific psychological tests like the Minnesota multiphasic personality inventory were not used. Therefore psychological problems which were not apparent in taking the case history but contributed to the erectile impotence may have been missed. In urological practice, a confirmative answer to the question of whether there are still spontaneous erections in the morning is taken to rule out an organic cause and therefore to suggest a psychological background of erectile impotence. This was the case in two of our patients, who, in addition to normal somatic test results, had positive evidence of major psychological problems. We could not determine a simple cause and effect relationship between the organic abnormalities found and the presence of erectile impotence. Significant correlations among the categories of our test battery could not be established. A set of different tests is therefore necessary to screen for abnormalities unrelated to each other but adding up to erectile dysfunction.

SYMPATHETIC SKIN RESPONSE

Figure 2 Examples of two patients with normal and absent sympathetic skin responses recorded in right hand and foot evoked by electrical stimuli applied contralaterally. For patient with absent responses only one out of several sweeps illustrated. Stimulation and beginning of responses indicated by arrows. Note long time base.

Figure 3 Examples of normal (left panel) and abnormal (right panel) heart rate variation measurements. In top traces 50 sweeps are superimposed. Position of cursors indicate minimal and maximal RR intervals, from which heart rate/min was calculated. Nine consecutive sweeps illustrating normal variability of RR interval in left in contrast to right panel are shown below.

Figure 4 Percentage of abnormal findings for neurological (A) and urovascular (B) investigations and for risk factors for vascular disease (C) and polyneuropathy (D). Clin Exam: clinical examination; NC Studies: nerve conduction studies; HRV: respiratory heart rate variation; SSR: sympathetic skin response; Pud SEP: pudendal somatosensory evoked potentials; BC Reflex: bulbocavernosus reflex; Diab mell: diabetes mellitus; Cor Heart Dis: coronary heart disease.

PREVALENCE OF NEUROLOGICAL ABNORMALITIES
Our patients varied widely in age so the question of whether ageing itself should be regarded as a risk factor for erectile impotence is relevant. Previous studies from 1948²³ concluded that the incidence of impotence in general is as low as 1.9% in 40 year old men

Figure 5 Numbers of patients with normal and abnormal findings in clinical neurological investigation, tests for autonomic dysfunction, and nerve conduction studies illustrated by flow chart in upper panel. Lower panel shows coincidence of abnormal findings among three autonomic tests (30/15 test, sympathetic skin response, heart rate variation).

but 25% in 65 year old men. These figures obviously relate to a sample which was not adequately tested for urological, vascular, or neurological dysfunction. In our series the number of pathological results in all categories of neurological and urovascular dysfunction increased with age, although the correlation did not reach the 95% level of significance. Therefore, the higher proportion of impotence among older men probably results from a higher incidence of risk factors and neurological or urovascular dysfunction in older men rather than from ageing itself.

Blaivas *et al*²⁴ found abnormalities of penile blood pressure in 67%, neurological abnormalities in 41%, psychiatric disorders in 35%, and a combination of abnormalities in 48% of their patients. The occurrence of neurological abnormalities was thus comparable to our results, even though they did not investigate autonomic nerve function electrophysiologically. In contrast, we were unable to confirm findings of Tackmann and Porst,²¹ who more often observed abnormalities of the bulbocavernosus reflex (BCR) (abnormal findings in 62 out of 122 patients tested) and of the pudendal SEP (abnormal in 31 out of 108 patients tested). For the BCR, similar results to ours were found by Wabrek.²⁵ Our data indicate that investigating BCR does not add greatly to the detection of neurological deficits and is therefore not necessary in the neurological workup.

Our study confirmed the previous finding that diabetes mellitus is a major risk factor for erectile impotence.²⁶ Whether the decisive abnormality in impotent diabetics is vascular occlusive disease²⁶ or diabetic neuropathy is still debatable.²⁷ The more common abnormalities of the BCR in diabetics²⁸ highlights pudendal neuropathy as the more important factor. From our data on a urological sample of patients with erectile impotence we can draw the following conclusions. Firstly, in most impotent men both neurological and urovascular abnormalities contribute to erectile dysfunction. In contrast CNS dysfunction is rarely a cause of erectile impotence. Secondly, with more than 50% of pathological findings for each category, history and clinical neurological evaluation of the peripheral sensorimotor and autonomic nervous system (NS) have the highest yield of pathological neurological results. The SSR in the foot was abnormal in a similar proportion of patients but it is known to be rather unspecifically abnormal in elderly patients.²² Thirdly, nerve conduction studies and BCR were abnormal in a third of the patients while pudendal SEPs did not provide additional evidence in identifying erectile impotence patients with neurological problems. All patients with abnormal nerve conduction results had neuropathic findings on clinical examination. This suggests that if a neuropathy causes or contributes to erectile impotence it must be clinically overt and not just detectable electrophysiologically. Finally, autonomic tests (30/15 test and HRV for evaluation of the parasympathetic NS and SSR in the hand for the sympathetic NS) were

abnormal in 64% of our patients. In most patients with signs of autonomic dysfunction abnormal results were found in both sympathetic and parasympathetic tests. More than 20% of the patients show abnormal autonomic tests in the absence of motor and somatosensory dysfunction.

DIAGNOSTIC STRATEGY AND THERAPEUTICAL IMPLICATIONS

Our results indicate that it is essential to use test screening for autonomic dysfunction. As sensorimotor polyneuropathy may mostly be detected clinically, nerve conduction studies are not always necessary. In addition, it is also unnecessary to perform a pudendal SEP in each patient. None of our patients with neurological involvement would have been missed if pudendal SEP had not been performed. We therefore suggest the following sequence of investigations in a patient with erectile impotence: exclude CNS disorders by clinical examination; evaluate peripheral NS clinically; and test autonomic sympathetic and parasympathetic NS. With erectile impotence being commonly (68%) associated with both urological and neurological abnormalities treatment of urovascular dysfunction—for example, by revascularisation—may not be sufficient or may even not be indicated in patients with severe neurological disturbances. Also, psychological therapy alone will obviously fail. Neurological dysfunction will remain undetected if appropriate tests of sensorimotor and autonomic function are not performed. Clearly most patients with erectile dysfunction have organic deficits. Therefore it is not justified to brand them as having a psychogenic disease.

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