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Application of Cardiac Autonomous Indices in the Study of Neurogenic Erectile Dysfunction

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Key Words

Baroreceptors · Blood pressure · Heart rate · Nervous system · Autonomic function

Abstract

A research area of increasing interest consists of studying the benefits of using spectral analysis to screen neurogenic erectile dysfunctions. Our hypothesis is that spectral analysis consists of a non-invasive and simple procedure to investigate such patients. Subjects were allocated into two groups: control, no erectile dysfunction (n = 17), and patients with erectile dysfunction (n = 15). RR intervals (RRI), systolic blood pressure, diastolic blood pressure and baroreflex sensitivity recordings were performed continuously in the supine position, followed by the seated position, and finally standing position. In the supine position, the control group had a higher RRI and a lower diastolic blood pressure. For frequency domain analyses of RRI in the supine position, the erectile dysfunction group had a higher normalized low-frequency (LF) index and low-frequency/high-frequency (LF/HF) ratio while showing a lower normalized HF index. In the seated position, the erectile dysfunction group presented a higher LF/HF ratio. Regarding systolic blood pressure, the erectile dysfunction group showed lower normalized LF and higher normalized HF indices only in the supine position. The α index in HF was lower in the erectile dysfunction group in the three positions. Spectral analyses of cardiac sympathovagal drive constitute a fruitful non-invasive approach to evaluate alterations in cardiovascular autonomic modulation in neurogenic erectile dysfunction patients.

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Introduction

Sexuality is a complex biopsychosocial process and physiological aspects of sexual response should be understood in the context of interpersonal and cultural factors [1, 2]. Erectile dysfunction is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse [1, 3]. Clinical studies show that erectile dysfunction may be caused by a variety of factors: psychogenic, arteriogenic, neurogenic, endocrinologic, and cavernosal, based on the organs that are involved in penile erection. Amongst them, neurogenic erectile dysfunctions are an important group of organic etiologies probably because a deficiency of neurotransmitters is the final common pathway in many diseases and conditions [1, 3, 4].

A research area of increasing interest consists of studying the benefits of using spectral analysis to screen for such abnormalities [5–8]. Indeed, spectral analyses of fluctuations in the intervals between consecutive heart beats (RR intervals) or in blood pressure (BP) are likely to provide information about cardiovascular neural regulation [9]. The support for using RR interval (RRI) variability as an index of autonomic cardiovascular control comes from data demonstrating that it is virtually abolished after parasympathetic and sympathetic blockades [10, 11]. Human and animal studies support the hypothesis that the low-frequency (LF) component of RRI could be used as a marker of sympathetic and vagal modulation to the heart, high-frequency (HF) component of RRI as a marker of cardiac vagal modulation and the LF/HF ratio of RRI as a marker of cardiac sympathovagal balance [10, 11].

Modern approaches to baroreflex analysis make it possible to evaluate the sensitivity of the spontaneous baroreflex using a non-invasive beat-by-beat measurement of BP and RRI [12]. These techniques are used particularly in the evaluation of the sensitivity of the cardiac baroreflex by analyzing the relationship between variations in systolic blood pressure (SBP) and RRI. Baroreflex sensitivity is expressed in ms/mm Hg and corresponds to a measure of the changes in RRI that are caused by changes in SBP [13, 14].

The present contribution aims at using spectral analysis to assess the sympathovagal drive of the heart for patients with neurogenic erectile dysfunction. The hypotheses under investigation are (i) neurogenic erectile dysfunction patients have an altered cardiac autonomic balance, and (ii) spectral analysis provides an efficient non-invasive and simple procedure to investigate such patients.

Subjects and Methods

Subjects

This study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki (2000) of the World Medical Association. After explanation of the experimental procedure, written informed consent was obtained from each subject.

The diagnosis and recruited patients with an erectile dysfunction, defined as insufficient rigidity of the penis for penetration, was made by a single urologist (B.C.). Staff members of Hospices Civils de Lyon, Université Claude Bernard and École Normale Supérieure de Lyon were recruited as a control group. The essential components of medical history were assessed and patients were not included in the study if they presented: smoking, hypertension, vascular dysfunction, peripheral pulse deficits, systemic or endocrine diseases, cardiovascular risk factors, cardiac, renal or hepatic dysfunction, neurological disease, endocrine disease, medications/recreational drug use, pelvic/perineal/penile trauma and surgery and pelvic radiotherapy. In the same way, patients with score of $\geq$16 on the Centre for Epidemiologic Studies Depression Scale were not included in the study [15]. All subjects underwent physical, neurological and psychiatric and urologic examinations. Subjects were allocated into two groups: control, no erectile dysfunction (n = 17), and patients with erectile dysfunction (n = 15). The mean duration of erectile dysfunction in this group was 4 years.

Erectile dysfunction was determined with the International Index of Erectile Function (IIEF) questionnaire [16]. 53% (8) of the patients had a mild erectile dysfunction (IIEF score between 17 and 25), 34% (5) had a moderate erectile dysfunction (IIEF score between 11 and 16), and 13% (2) had severe erectile dysfunction (IIEF score between 10 and 1). All patients of the control group had an IIEF score >26.

Another neurological examination was performed in the erectile dysfunction group to identify evidence of alternative neurological disorders, not identified by history. Each patient with erectile dysfunction underwent hormonal evaluation (testosterone and prolactin blood level) which was normal and a penile pharmaco-Doppler ultrasound Doppler considered as normal. Perineal electrophysiological studies were performed only in patients with erectile dysfunction to establish the neurogenic origin of erectile dysfunction. Patients with historical or examination evidence of a neurological disorder other than peripheral neuropathy were excluded from the study.

Data Collection

Each participant was asked to refrain from drinking coffee and tea in the 24 h preceding the experimental session. Recording sessions took place between 09:00 and 12:00 h in a quiet room.

The RRI time in milliseconds between two R peaks on the electrocardiogram (ECG) was obtained from a standard bipolar ECG lead and an R-peak detection circuit with precision of 1 ms. SBP and DBP (diastolic blood pressure) were obtained by finger photoplethysmography (Finapres ppTNO; Biomedical Instrumentation Research Unit, Amsterdam, The Netherlands). Heart rate and BP were also monitored during the test independently of data collection with an ECG monitor and an automated oscillometer (Dynamap™; Criticon Inc., Tampa, Fla., USA). Breathing was quantified by a device constructed in our laboratory. This

Table 1. Demographic characteristics of the 41 subjects included in the study

Group	Control	Erectile dysfunction*
Number	17	15
Age, years	52 ± 7	55 ± 9
Weight, kg	75 ± 3	77 ± 7
Body mass index, kg/m^2	24 ± 1	24 ± 2

Data are expressed as median ± median absolute deviation.
* Non-parametric Mann-Whitney test: $p < 0.05$ vs. control group.

device uses comfortable elastic bands, which do not restrict breathing movements, wrapped around the rib cage and abdomen to measure thoracic and abdominal displacements during breathing. Continuous data acquisition (ECG, BP and respiration) at a sampling rate of 1,000 Hz (ECG, BP) and 500 Hz (respiration), were done on a PC Pentium™ 133 MHz with a 12-bit analogue-to-digital converter (AT-MIO-16E-10™; National Instruments, Austin, Tex., USA) equipped with a software developed with LabVIEW 4.0.1 software AA (National Instruments, Austin, Tex., USA).

Neurophysiologic Investigation

Electromyogram recordings were obtained with a Medelec Sapphire Premiere™ (Vickers Medical, Old Woking, Surrey, UK). The erectile dysfunction group had perineal electrophysiological studies including: bulbocavernosus reflex latency studies, left and right bulbocavernosus muscle electromyography, somatosensory-evoked potentials of the pudendal nerve, measurement of sensory conduction velocity of the dorsal nerve of the penis, and determination of pudendal nerve terminal motor latencies [3, 17, 18].

Experimental Protocol

RRI, BP and respiratory frequency recording were performed continuously over three periods: supine position (15 min), followed by seated position (15 min), and finally standing position (15 min). These postural changes provoke instantaneous changes in heart rate and BP, mainly resulting of autonomic modifications [19, 20]. If presyncopal or syncopal symptoms occurred (a feeling of faintness), rapid drop in SBP (>25 mm Hg) or tachycardia (>160 beats/min), the test was interrupted before the end of the 15 min.

Preprocessing

The transformation of the recorded data into a time series, to which spectral analysis can be applied, requires the following preprocessing steps. A sliding-window median filter is first applied to the RRI and SBP series to replace outliers and/or abnormal values with a local average. RRI and SBP series are independently resampled on a regular grid, at sampling frequency: fe = 10 Hz. It is chosen a priori high with respect to the *naturally* expected frequency content of the data (around a few Hz). It is checked a posteriori that Shannon criterion is well satisfied. A standard linear detrending procedure is systematically applied independently on both time series. To finish with, the data are high pass filtered. The cut-off frequency is: fc = 0.025 Hz. The spectral powers were split into three frequency bands: very low frequency (VLF, 0.025–0.040 Hz), low frequency (LF, 0.040–0.150 Hz), and high frequency (HF, 0.150–0.400 Hz).

Baroreflex Sensitivity

We proposed to compute two dynamic gains accounting for the transfer function between RRI and SBP using non-parametric spectral estimation tools involving cross-spectrum analysis between RRI and SBP [21]. For each frequency band (HF and LF) estimates of power spectral density for SBP and RRI using Welch's averaged periodogram method is performed and the α gains are computed. There is no consensus on which frequency band should preferably be used. According to some authors, the LF band is more specific of the baroreflex activity, while for others, HF variations in RRI and SBP also depend on the baroreflex and study more specifically on the influence of the respiration over the baroreflex [9]. Autonomic indices are also computed in order to evaluate the sympathovagal balance: the HF normalized index (HFn = spectral power of HF/(LF + HF)) reflects the parasympathetic influence on the heart rate, the LF normalized index (LFn = spectral power of LF/(LF + HF)), even if controversial, may reflect the sympathetic influence on the heart rate, and the ratio of LF/HF may reflect the sympathovagal balance influence on the heart [22].

Statistics

The Mann-Whitney test was used to compare demographic characteristics (age, weight, body mass index) between groups. The linear mixed model was used for the analysis of longitudinal data. Linear mixed models allow the study of the different effects that could impact the data and, at the same time, consider different sources of variation using random effects and/or covariances structures [8, 23]. In this case the model for each studied parameter includes the main health and body position effects and their interactions. The covariance structure that best fit the data was chosen based on the likelihood ratio test. Then inference about the effects of interest was based on the chosen models to detect changes in RRI, SBP, respiratory frequency, baroreflex sensitivity and spectral powers between successive periods within each group of patients [8, 22, 23].

Fisher exact test is performed to compare nominal data. All results are expressed as median ± median absolute deviation. p values lower than a 0.05 chosen level are regarded as statistically significant.

Results

Demographic and Clinical Characteristics

Table 1 outlines the demographic characteristics of the patients included in the study. The two groups are similar with respect to age, weight and body mass index. Time domain measures of RRI, respiratory frequency, SBP and DBP during changing positions are presented in table 2.

Table 2. Time domain measures of RRI, SBP, DBP and respiratory frequency in different experimental conditions

	Supine position	Seated position	Standing position
RRI, ms			
Control (n = 17)	979 ± 98	889 ± 107**	741 ± 90**
Erectile dysfunction (n = 15)	838 ± 110*	794 ± 106	708 ± 71**
SBP, mm Hg			
Control (n = 17)	109 ± 8	120 ± 9**	117 ± 12**
Erectile dysfunction (n = 15)	115 ± 22	137 ± 20**	140 ± 19**
DBP, mm Hg			
Control (n = 17)	55 ± 6	70 ± 7**	69 ± 7**
Erectile dysfunction (n = 15)	66 ± 11*	78 ± 10**	76 ± 5**
Respiratory frequency, rpm			
Control (n = 17)	12 ± 1	13 ± 1	13 ± 1
Erectile dysfunction (n = 15)	12 ± 1	12 ± 1	13 ± 1

RRI = RR intervals; n = number of patients; SBP = systolic blood pressure; DBP = diastolic blood pressure; rpm = respiration per minute. Data are expressed as median ± median absolute deviation.

* Linear mixed model; $p < 0.05$ vs. control. ** Linear mixed model; $p < 0.05$ vs. supine position.

Table 3. Normalized frequency domain measures of RR intervals in different experimental conditions

	Supine position	Seated position	Standing position
LFn, %			
Control (n = 17)	62 ± 2	73 ± 9**	86 ± 4**
Erectile dysfunction (n = 15)	76 ± 11*	81 ± 7**	89 ± 4**
HFn, %			
Control (n = 17)	38 ± 2	27 ± 10**	14 ± 4**
Erectile dysfunction (n = 15)	24 ± 11*	19 ± 7**	11 ± 4**
LF/HF			
Control (n = 17)	1.61 ± 0.07	2.63 ± 0.07**	6.25 ± 0.05**
Erectile dysfunction (n = 15)	3.22 ± 0.02*	4.34 ± 0.04*, **	7.69 ± 0.07**

Normalized power was obtained by dividing the cumulative power within each frequency band (low frequency or high frequency) by the sum of low frequency and high frequency. LFn = Normalized low frequency; HFn = normalized high frequency. Data are expressed as median ± median absolute deviation.

* Linear mixed model; $p < 0.05$ vs. control. ** Linear mixed model; $p < 0.05$ vs. supine position.

In the control group, the seated position significantly reduces RRI (by 9%) and significantly increases SBP and DBP (by 10 and 27% respectively). The standing position, compared to the supine position, significantly reduces RRI (by 24%) while it significantly increases SBP and DBP (by 7 and 25% respectively).

In the erectile dysfunction group, the seated position significantly increases SBP and DBP (by 19 and 18% respectively). The standing position, compared to the supine position, significantly reduces RRI (by 15%) and significantly increases SBP and DBP (by 22 and 15% respectively). Regarding comparisons between groups, RRI and DBP significantly differ only in the supine position, where the control group has a higher RRI and a lower DBP (table 2).

Normalized frequency domain analyses of RRI are reported in table 3. In the supine position, the erectile dysfunction group has a higher LFn and LF/HF ratio while

Table 4. Normalized frequency domain measures of systolic blood pressure in different experimental conditions

	Supine position	Seated position	Standing position
LFn, %			
Control (n = 17)	87 ± 4	75 ± 6**	83 ± 5
Erectile dysfunction (n = 15)	79 ± 8*	80 ± 9	85 ± 5**
HFn, %			
Control (n = 17)	13 ± 4	25 ± 6**	17 ± 4
Erectile dysfunction (n = 15)	21 ± 8*	20 ± 9	15 ± 5

Normalized power was obtained by dividing the cumulative power within each frequency band (low frequency or high frequency) by the sum of low frequency and high frequency.

LFn = Normalized low frequency; HFn = normalized high frequency. Data are expressed as median ± median absolute deviation.

* Linear mixed model; $p < 0.05$ vs. control. ** Linear mixed model; $p < 0.05$ vs. supine position.

showing a lower HFn. In the seated position, the erectile dysfunction group presents a higher LF/HF ratio. Seated and standing positions, compared to the supine position, increase LFn, LF/HF ratio and decrease HFn in both groups. Regarding SBP, comparisons between groups only showed a difference in the supine position (table 4). The erectile dysfunction group shows a lower LFn and a higher HFn.

In the seated position compared to the supine position, there was decreased LFn and increased HFn only in the control group. In the standing position compared to the supine position, there was increased LFn only in the erectile dysfunction group. In the standing position, compared to the supine position, there were decreases in αLF in both groups, while in the seated position decreases in αLF only in the control group. Changing position from supine to seat and to standing decreased αHF in the control group (table 5). The standing position compared to the supine position decreased αHF in the erectile dysfunction group. αHF is lower in the erectile dysfunction group compared to the control group in the three positions.

Discussion

Erectile dysfunction is a global problem whose prevalence tends to increase with population age. Data from the Massachusetts Male Aging Study indicated that the prevalence of erectile dysfunction of any degree is 39% for 40-year-old men, and 67% for those aged 70 years [24].

It has been estimated that 10–19% of erectile dysfunctions are of neurogenic origin and multiple factors may be responsible for neuropathy of erectile dysfunction [25–27]. Penile erection is a complex event involving integration of psychological, neurological, endocrine, vascular and local anatomic systems. The innervation of the penis is both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor). The sympathetic and parasympathetic nerves merge from the neurons in the spinal cord and peripheral ganglia to form the cavernous nerves, which enter the corpora cavernosa and corpus spongiosum to affect the neurovascular events during erection and detumescence. The sensation and the contraction of the bulbo- and ischiocavernosus muscles are assured by the somatic nerves [4].

Many tests are available to evaluate the motor efferent nerves to the perineum as well as the sensory afferent nerves from the penile skin [3, 18, 25]. The problem with many of these tests is that they do not measure autonomic function directly, and clinicians should be cautious in making the diagnosis of neurogenic erectile dysfunction [3, 18, 25, 26]. For example, the electrophysiologic bulbocavernosus reflex is a response that is recorded from the bulbocavernosus muscle after electrical stimulation of the pudendal nerve, usually on the penis. It is a measure of somatic penile innervation, whereas erection is primarily dependent on autonomic function [28]. Therefore, markers capable of dynamically assessing autonomic drive would be important diagnostic tools.

The non-invasive nature of frequency domain techniques permits measurement under a broad range of conditions like the evaluation of erectile dysfunction [5–8, 29]. In a recent article, we demonstrated the interest of a generalized linear mixed model framework to assess differences between no erectile dysfunction and patients with erectile dysfunction [8]. In the frequency domain, our analysis suggests an alteration in autonomic cardiac regulation in patients with erectile dysfunction (table 3). This is manifested by the significant difference between groups in the LF/HF ratio in the supine and seated position as well as in normalized LF and HF in the supine position. These results are similar to the findings reported by Lavie et al. [29], stating that patients complaining of daytime sexual dysfunction have altered cardiac autonomic balance. Lavie et al. [29] showed that in patients with organic erectile dysfunction there is a relative decrease in the activity of the parasympathetic division combined with a dramatic increase in the activity of the

Table 5. Baroreflex sensitivity (α index) in low frequency and in high frequency in different experimental conditions

	Supine position	Seated position	Standing position
αLF, ms/mm Hg			
Control (n = 17)	0.38 ± 0.10	0.30 ± 0.06**	0.22 ± 0.07**
Erectile dysfunction (n = 15)	0.29 ± 0.12	0.29 ± 0.18	0.16 ± 0.07**
αHF, ms/mm Hg			
Control (n = 17)	1.64 ± 0.49	0.82 ± 0.26**	0.41 ± 0.11**
Erectile dysfunction (n = 15)	0.58 ± 0.32*	0.50 ± 0.20*	0.24 ± 0.17*, **

αLF = α index in low frequency; αHF = α index in high frequency. Data are expressed as median ± median absolute deviation.

* Linear mixed model; $p < 0.05$ vs. control. ** Linear mixed model; $p < 0.05$ vs. supine position.

sympathetic division during sleep. This was manifested by significant differences between the LF/HF ratio as well as the LF and HF power.

In our study there is no difference between groups in the seated or standing position, however LF and HF do not necessarily quantify the autonomic nervous system [9, 30]. The possibility that sympathetic reactivity might operate somewhat independently of basal sympathetic activity is supported by some studies [31]. This sympathetic dominance is also found by the others; in patients with organic erectile dysfunction there are alterations in the balance between the sympathetic and parasympathetic division [29, 32, 33].

For young adults, an increase of 10 mm Hg in BP on standing identifies a group at increased risk of developing hypertension over the subsequent 8 years [19, 31]. The erectile dysfunction group has a greater increase in SBP (22%) compared to the control group (7%) after changing position from supine to standing. Such a pressure response should be analyzed with respect to incident cardiovascular diseases. It is acceptable to assume that an increased sympathetic drive may contribute to the initiation of cardiovascular events, particularly arrhythmias and myocardial infarction, that occur in the context of a high level of sympathetic activation and are likely to have poorer outcomes [22, 33]. This could be meaningful when using treatment like sildenafil that causes a marked increase in sympathetic activation, evident both at rest and during physical, mental and metabolic stress [34]. The specificity of SBP LF powers in reflecting sympathetic activation is limited because these components are also affected by resonance in baroreflex loop [9, 35].

We measured cardiac spontaneous baroreflex sensitivity with a frequency domain technique using a time-frequency approach in order to analyze the effects of changing position more precisely. We retained a coherence criterion >0.1, as suggested by other authors [36]. Changing position reduces baroreflex sensitivity in both groups, but the erectile dysfunction group has a lower αHF compared to the control group (table 5).

We noted a decrease in the α index of the HF band after position changes (within groups) and between groups (for the same position), suggesting a diminished HF component of baroreflex gain. In addition, we observed no significant difference in the respiratory frequency (about 13 breaths/min) after position changes (within groups) and between groups (for the same position). αLF gain does not significantly differ between groups, although there is a tendency towards a lower αLF in the erectile dysfunction group (table 5).

Study Limitations

Complex interactions exist between the two components of the cardiac autonomic nervous system, and the finding that normalized LF increased and normalized HF decreased with standing indicates that these variables solely contain broad information about autonomic outflows but do not necessarily quantify them [30]. However, cardiovascular variabilities are thought to be valid indices of autonomic outflows because they provide valuable prognostic information, represent a non-invasive window into autonomic control, have a possible clinical application and are simple and cheap methods [30, 37]. The assessment of the baroreflex sensitivity used in our study

only analyzed the cardiac baroreflex and not the arteriolar baroreflex. The amplitude of the RRI and SBP study remains limited, but because of a rather short sliding window, this range could be a little extended in case of increasing changes in RRI and SBP [21]. Therefore, in view of the criticism of RRI and SBP variability methodology to obtain a differential diagnosis of neurogenic erectile dysfunction, our data suggest that they could add valuable diagnostic information.

Since neurologic erectile dysfunction may be related to many causes, we eliminated trauma, chronic diseases, surgery, and neural malformation, and studied patients with idiopathic neurologic erectile dysfunction. So, our sample size was small, but patients with neurogenic erectile dysfunction without endocrine or neurological disease are rare in our hospital.

Although we try to not include depressive patients, we are unable to deal with the presence of depressive episodes related to negative aspects of sexual functioning [32]. Respiratory frequency and tidal volume were not constrained in this study, because the conscious mental effort to control both respiratory frequency and tidal volume may in itself alter autonomic activity [38, 39]. Moreover, it has been previously found that changes in tidal volume are less important than breathing frequency [40, 41].

In conclusion, our results show that spectral analysis of cardiac sympathovagal drive used in neurogenic erectile dysfunction patients may be an interesting non-invasive and relatively simple approach. Further studies are necessary for accurately evaluating whether spectral analysis might be proposed for discriminating between neurogenic and other causes of erectile dysfunction.

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