Rhythmic Oscillations of Human Penile Bioimpedance in Healthy Individuals and in Patients with Vascular Erectile Dysfunction

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Small variations of electric impedance (bioimpedance) of human penis were examined in healthy volunteers and in patients with vascular erectile dysfunction (ED). The harmonic analysis revealed rhythmic oscillations of penile bioimpedance at frequencies corresponding to the heart and respiration rates and Mayer wave (0.1 Hz) and to multiple frequencies (harmonics) of the respiratory and cardiac oscillations. In normal penile bioimpedance spectrum, the Mayer and respiratory peaks were several times higher than the first cardiac (pulsatile) harmonic indicating neurogenic origin of rhythmic bioimpedance variations in the whole penis. The most of healthy individuals (78%) demonstrated the cardiac harmonics at the frequency range of 4-7 Hz that violated the monotone decrement of the pulsatile harmonic series suggesting the resonant character of oscillations of the penile arteries at this "near" frequency range. In contrast to stable 1-4 cardiac harmonics, the amplitudes of the near-range resonant harmonics could vary during few minutes suggesting a causal relation of the corresponding bioimpedance oscillations with the varying vascular tone in penile arteries. The most patients (89%) with vascular ED demonstrated not only the first 1-4 monotonically decrementing harmonics and the near-resonant ones, but also the stable cardiac harmonics at the "far" frequency range of 8-14 Hz that also disturbed the monotonic character of the cardiac harmonic series indicating the sclerotic alterations in regional arteries. In ED patients, insignificant decrease of the initial cardiac harmonics C1-C3 in comparison with the norm was accompanied by pronounced and significant decrease of the respiratory R1 and Mayer M1 peaks. The study showed that the far-frequency bioimpedance resonances at the range of 8-14 Hz and dramatic drop of Mayer and respiratory peaks are the diagnostic signs of vascular ED independent on the accompanying hormonal or neurogenic disorders.

Key Words: *bioimpedance harmonic analysis; erectile dysfunction; Mayer wave; resonant bioimpedance oscillations; penile atherosclerosis*

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Deficiency in blood supply to lower urinary pathways and reproductive organs developed due to obstruction of the arterial bed underlies numerous and widely spread pathological states, erectile dysfunction (ED) included. Penile erection is a predominantly vascular phenomenon, which finalizes the integrated and synchronous action of neurovascular, transmitter-lacunar

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and hormonal mechanisms responsible among other tasks for the reproductive function of the male organism. Special complicacy of ED treatment is explained by the fact that this disease can originate not only from the vascular deficiency, but also from neurogenic, psychogenic, and hormonal abnormalities [1,3]. The strategy of ED treatment is determined by the nature of the above disorders underlying the disease. Of particular importance in this strategy is revealing and refining the vascular pathology of the penis.

At present, the ultrasonic examination of the penis with intracavernous pharmacological testing is the most widely spread assessment of the arterial bed in the cavernous body [3,8]. The basic limitation of the echography methods is the lack of a precise criterion to differentiate the moderate alterations of the arterial endothelial function responsible for variations of vascular lumen caused by the changes in tensile strength at the arterial wall from pathological waning of this ability. The sonographic methods are characterized with small resolving power to measure the blood flow in arteries situated in the depth of an organ. Moreover, the data depend on the mutual position of arterial trunk and the sonic transmitter-receiver axis. Variations in the geometry of vascular bed in various patients degrade the accuracy of blood flow data obtained with the ultrasonic methods [1]. The bioimpedance methods are free from these limitations, and they can recorder the changes in the electrical parameters of the tissues in the whole organ (specifically, in penis) which is explained by different mechanisms employed by electric current and sonic waves to pass across biological tissues [6,11].

The spectacular development of electronics and computing technique in the last decade radically widened the diagnostic scope of the routine rheography. Now it is possible to measure microvariations in the impedance of biological tissues and perform the harmonic (Fourier) analysis of the long epochs of these variations encompassing hundreds cardiac cycles. The novel tools revealed not only the pulsatile (cardiac) harmonics, but also the bioimpedance oscillations at low frequencies corresponding to respiratory rate and Mayer wave [4,5,15]. Even in its reduced version employing only one cardiac cycle, the harmonic analysis of bioimpedance could detect atherosclerosis in human legs [14], hepatic diseases [7], and the pronounced alterations in the structure of the pulse wave in the major arteries during hypertension [10]. The multicycle harmonic analysis (with long epochs containing dozens of cardiac cycles) could assess the regional visceral neural influences in rat urinary bladder based on spectrum peaks of bioimpedance variations at respiration rate and Mayer periodicity [4,15].

Our aim was to test the possibility to employ the long-epoch harmonic analysis of bioimpedance variations to reveal vascular pathology of human penis during vascular ED.

MATERIALS AND METHODS

The study was carried out with the help of the custom-made hardware–software system including a high-resolution low-noise impedance converter capable to record not only the large-scale bioimpedance changes caused by pulsatile oscillations of the blood pressure but also the small variations of bioimpedance of diverse origin [4,5,15]. The resolving powers of the impedance converter in the channels of total ("basal") impedance and alternating impedance component were 50 milliΩ in the range of 0-1000 Ω and 250 microΩ in the range of ±4 Ω, respectively. The basal impedance channel was employed to control the contacts of the electrodes, while the alternating impedance channel recorded the bioimpedance variations. The hardware–software system incorporated the analog and software band filters to isolate the analyzed frequency band within 0.05-15.00 Hz and the notch filter to eliminate the industrial electric noise at 50 Hz, which made it possible to carry out the measurement in routine clinical environment.

An original 4-channel AD convertor digitized the signals at the sampling rate of 16 kHz in each channel. The on-board microprocessor decimated the digitized signals to the rate of 160 Hz. The digitized signals were passed across a galvanic isolator (breakdown voltage 2.5 kV) to a PC via an USB port.

To obtain the amplitude spectrum of bioimpedance oscillations with fast Fourier transform, the record of alternating impedance component was cut into the epochs of a certain length. The epoch of 25.6 sec (4096 data points) was used to obtain the "survey" spectrum with frequency resolution of 0.04 Hz necessary to analyze the low-frequency variations of bioimpedance at Mayer and respiration rates. The epoch of 12.8 sec (2048 data points) was used to analyze the cardiac (pulsatile) bioimpedance harmonics with frequency resolution of 0.08 Hz. The spectra were calculated with Hanning window. In experimental records, the fragments were chosen that contained no artifacts caused by the involuntary movements. Such fragments included 1 to 4 epochs of the above length. The amplitude spectra of few epochs in the selected fragment were averaged. The result of Fourier transform was plotted as a dependence of amplitude of the periodic bioimpedance components on frequency.

To recorder bioimpedance in the bipolar manner, two ring non-polarizing Ag/AgCl electrodes made of silver wire 0.4 mm in diameter were mounted on radix penis and the coronal sulcus. The sterile gauze collars

were place above the electrodes and irrigated with physiological saline. The non-polarizing electrodes were used to diminish the electric noise during the measurement of bioimpedance microvariations [5]. The rheophallogram was recorded during 5-6 min in supine position under the silence.

RESULTS

The study was performed on healthy volunteers (N=18) and patients with ED (N=28) aging 18-76 years. The degree of erectile function disturbances and the signs of androgenic deficiency were assessed with AMS questionnaires and the scale of Morley. All the patients were subjected to penile echodopplerography combined with pharmacological probes, which revealed a drop in the linear blood velocity (N=13) in the penile arteries below 22 cm/sec and enhancement of resistance index to 0.85 and higher values. The accompanied hormonal disturbances were revealed with laboratory diagnostics by deficiency of sex hormones. The neurogenic abnormalities in ED patients were established by anamnestic data (the compromised neurological component included), weakening of perineal cutaneous sensitivity, hyporeflexia of the bulbocavernous or anal reflexes documented with electromyography of perineal muscles and the measurements of corticospinal tract conductivity. The clinical examinations subdivided the patients into three groups with vascular (N=13), vasculo-hormonal (n=10), and neurovascular (N=5) ED.

Figure 1 shows the survey (complete) spectrum of normal penile bioimpedance in the frequency band 0.05-15.00 Hz (epoch 25.6 sec). The spectrogram contains a relatively high low-frequency peak M1 at about 0.1 Hz assumed to be related to Mayer wave [13] and equally pronounced respiratory peak R1 recorded at the respiration rate. In addition, the spectrogram demonstrates pronouncedly smaller second respiratory harmonic R2 situated at the 2-fold respiration frequency and a set of cardiac (pulsatile) harmonics C1-C7 corresponding to the fundamental and multiple frequencies of the heartbeat.

A salient feature of the spectrum plots is the paradoxical great heights of the peaks M1 and R1, which were several times larger than the greatest (fundamental) cardiac (pulsatile) harmonic C1 (Fig. 1, *a*; Fig. 2, *a*; Table 2). Similar feature was observed in the experiments with rat urinary bladder [4]. It is an established fact that the spectrum peaks M1 and R1 in human major arteries are several times less than the height of fundamental pulsatile harmonic [5]. The above "inverse" (in comparison with the major arteries) relation between the heights of M1 and R1 peaks, on the one hand, and the height of C1 peak, on the other hand, which is characteristic of human penis in

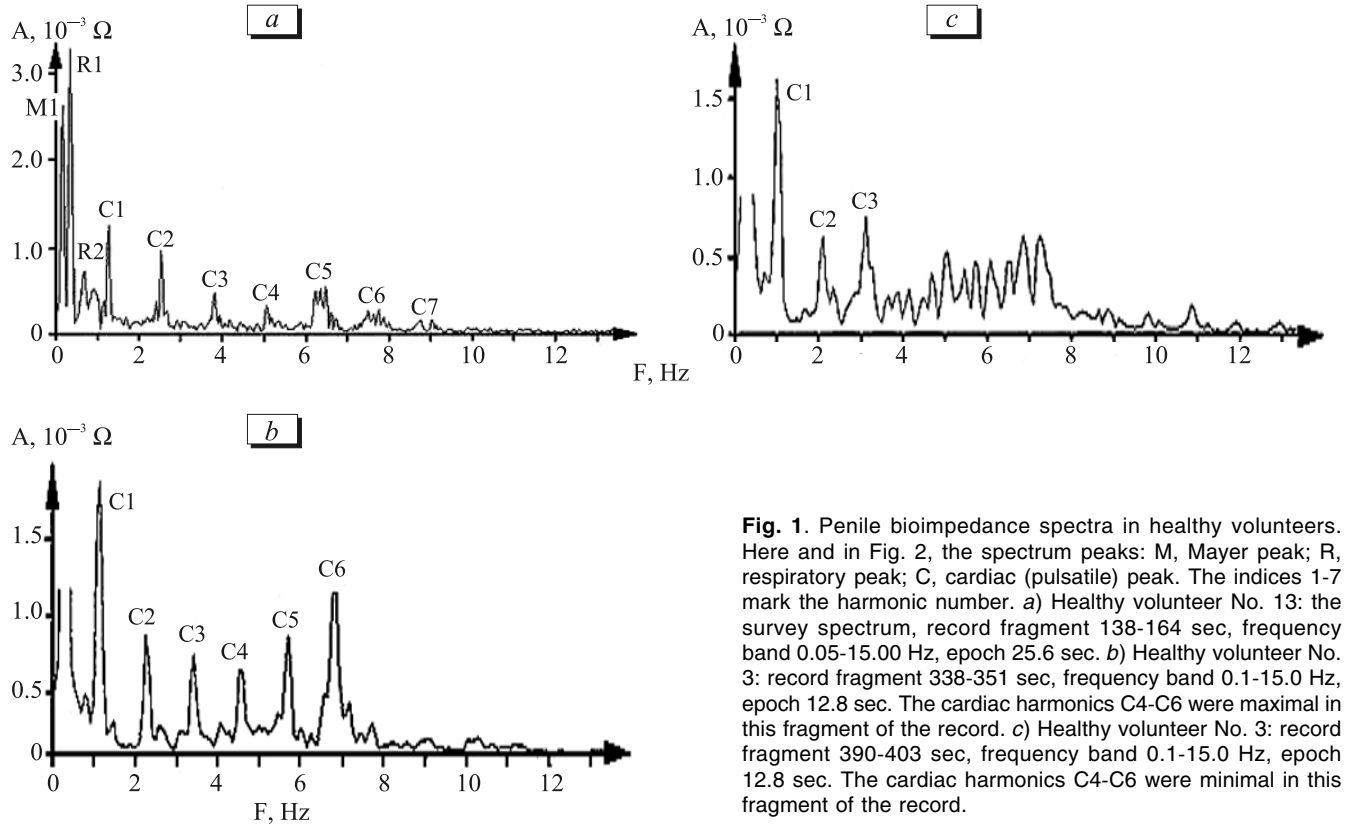

Fig. 1. Penile bioimpedance spectra in healthy volunteers. Here and in Fig. 2, the spectrum peaks: M, Mayer peak; R, respiratory peak; C, cardiac (pulsatile) peak. The indices 1-7 mark the harmonic number. *a*) Healthy volunteer No. 13: the survey spectrum, record fragment 138-164 sec, frequency band 0.05-15.00 Hz, epoch 25.6 sec. *b*) Healthy volunteer No. 3: record fragment 338-351 sec, frequency band 0.1-15.0 Hz, epoch 12.8 sec. The cardiac harmonics C4-C6 were maximal in this fragment of the record. *c*) Healthy volunteer No. 3: record fragment 390-403 sec, frequency band 0.1-15.0 Hz, epoch 12.8 sec. The cardiac harmonics C4-C6 were minimal in this fragment of the record.

TABLE 1. Incidence of Resonant Impedance Oscillations in Human Penis in Healthy Volunteers and Patients with Vascular ED

Group	Number of examined persons		Without resonances		Resonances:					
					only near		near and far		only far	
	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
Healthy volunteers	18	100	4	22	11	61	3	17	0	0
ED*	28	100	2	7	1	4	23	82	2	7

Note. The experimental group comprised the patients with isolated or combined (with hormonal and/or neurogenic disorders) vascular ED.

the norm, cannot be explained by mere the rhythmic oscillations of penile arteries caused by neural control of their tone. Most probable, the observed rhythmic oscillations of penile bioimpedance at Mayer and respiratory rate results from the regional influences of ANS exerted on the entire penile tissue in addition to its vasculature. Such neurogenic changes in the impedance of the entire penile tissues (reflected by M1 and R1 peaks) are several times greater than the bioimpedance variations caused by the changes in penile vascular bed reflected by the pulsatile harmonics (Table 2).

To analyze the cardiac (pulsatile) variations of penile bioimpedance, the frequencies below 0.1 Hz were rejected, and the epoch was halved to 12.8 sec. Fig. 1 (*b*, *c*) shows the fragments of penile bioimpedance spectrum in the norm, which encompass only the cardiac harmonics. In analysis of these harmonics, it should be taken into consideration that in healthy individuals, the amplitudes of bioimpedance pulsatile harmonics of finger [5], an arm along the course of the radial artery [10], foot [14], and liver [7] constitute a monotonic decreasing series. This monotony of the harmonic series reflects both the initial structure of the pulsatile pressure wave in the aorta with major arteries and the predominant damping of the high-frequency oscillations in arterial pressure as the pulsatile wave spreads across the arterial tree [2]. Thus, the pronounced decrease in the amplitude of the higher cardiac harmonics at the periphery of the blood system in any organ is an expected and clear phenomenon. This view dramatically contradicts to the pronounced violation of monotony in the pulsatile harmonic series C1-C7 established in most healthy indiciduals (78%; Table 1; Fig. 1, *b*, *c*). This violation demonstrated itself by appearance of a group of spectrum peaks whose heights increased with the harmonic number (for example, C4<C5<C6 in Fig. 1, *b*). At this, the first three cardiac peaks C1-C3 always decreased in a monotonic manner with harmonic number (C1>C2>C3) and were rather stable. In contrast, the "monotony violators" C4-C7 could vary in the same subject during the few minutes of record (Fig. 1, *b*, *c*).

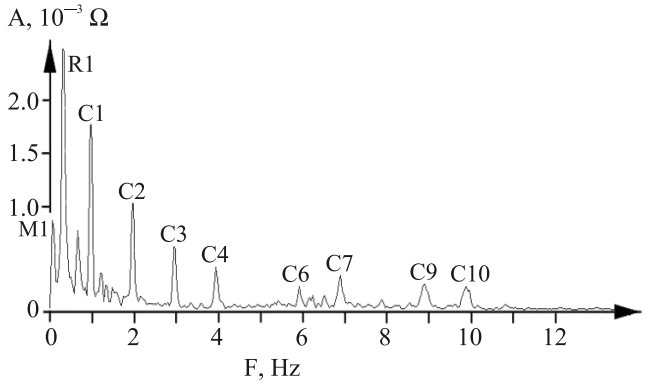

Fig. 2. Typical penile bioimpedance survey spectrum of patient No. 26 with vascular ED. The record fragment 110-136 sec, frequency band 0.05-15.0 Hz, epoch 25.6 sec.

In the most normal subjects (83%), there were no pulsatile peaks with the number C8 and higher (Table 1). In some healthy persons (22%), the cardiac bioimpedance oscillations were represented by only C1-C3 harmonics. Thus, a typical feature of penile bioimpedance in the control group was the presence of the pulsatile spectrum peaks in the frequency range 3-7 Hz that violated monotony of the harmonic series.

The data obtained can be interpreted in the following way. The arterial pulse wave invading the penis is composed of harmonic series of pulsatile oscillations at the fundamental and multiple frequencies of the heartbeat, whose amplitudes are normally monotonically decrease with the harmonic number. In the major human arteries, it is possible to reveal at least ten cardiac (pulsatile) harmonics, so the absence of C4 and higher pulsatile harmonics in some healthy subjects indicates greater damping properties of the penile arteries in these persons than those in some healthy individuals demonstrating pulsatile harmonics up to C7.

Since damping of the pulse wave in the arteries decreases with elevation of arterial wall rigidity [2], the existence of C4-C7 harmonics in some healthy individuals means enhanced rigidity (or decreased elasticity) of their penile arteries in comparison with other healthy volutneers that had no such harmonics. This hypothesis explains the presence of C4-C7 harmonics in some subjects but not their paradoxically high amplitude disturbing the monotony of the pulsatile harmonic series characteristic of the pulse wave in the major arteries, which can only become more pronounced due to damping properties of the arterial tree. Probably, the abnormally high C4-C7 peaks comparable by the height to the first (fundamental) cardiac harmonic, reflect the resonant radial oscillations of the penile arteries in the corresponding frequency range (4-8 Hz) in some healthy volunteers caused by enhanced rigidity of these arteries.

The aorta with major arteries is considered as a hydromechanical system with moderately damped natural (intrinsic) oscillations [12]. The non-monotony series of the normal penile pulsatile harmonics and similar data on hepatic pulsatile harmonics during pathology [7] can be viewed as indications on the possibility of resonant phenomena not only in the proximal, but also in the distal subdivisions of the arterial tree.

The observed fact that the resonant oscillations of penile bioimpedance could appear and disappear during a single record lengthening for few (3-6) minutes attests to the changes in rigidity of the penile arteries, which can reflect changes in neurogenic (sympathetic) vascular tone during examination. Taking into consideration that the heart rate differed in individual persons, the observed resonant oscillations of penile bioimpedance in healthy volunteers can be more precisely characterized not with the harmonic number, but with the frequency range of 3-7 Hz. In the following, the resonances at this frequency band will be referred to as the "near" ones.

Figure 2 shows typical spectra observed in patients with vascular ED. In some of these patients,

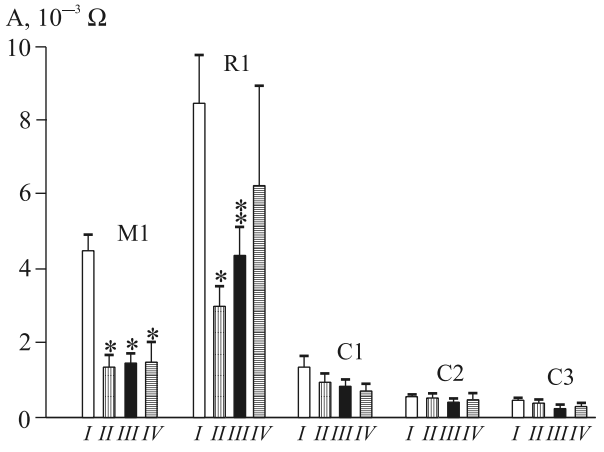

Fig. 3. The amplitude of spectrum peaks of penile bioimpedance in normal subjects and in ED patients. *I*: Norm; *II*: vascular ED; *III*: vasculo-hormonal ED; *IV*: vascular ED with neurogenic component. The spectrum peaks: M, Mayer peak; R, respiratory peak; C, cardiac (pulsatile) peak. The indices 1-3 mark the harmonic number. **p*<0.01, ***p*<0.05 in comparison with norm.

the survey spectrum demonstrated not only the "near" resonant pulsatile harmonics, but also the "far" resonant bioimpedance oscillations at the frequency range of 8-14 Hz. The frequency band of 7-8 Hz was the intermediate, which separated the near and far bioimpedance resonances. Thus, the healthy subjects significantly differ from the patients with vascular ED by the absence of the far resonances (22+61=83% in the norm) or their presence (82+7=89% in patients with vascular ED, Table 2). In contrast to the near resonances, the far ones were stable during the recording period of 3-6 min. Elevation of the resonant frequency of the penile arteries in patients with vascular ED in comparison with the norm indicates increased rigidity of these arteries. It is noteworthy that increased rigidity of the major arteries was observed during atherosclerosis [9]. Stability of the far penile resonances is an argument against their neurogenic origin that otherwise could be explained by an increase in rigidity due to dramatic but reverse increment of the vascular

TABLE 2. Bioimpedance Spectrum Peak Heights of Human Penis in Healthy Volunteers and in Patients with Erectile Dysfunctions of Diverse Genesis (*M*±*SEM*, mΩ)

Group	M1	R1	C1	C2	C3
Norm (*N*=18)	4.5±0.4	8.5±1.3	1.3±0.3	0.6±0.2	0.5±0.2
VED (*N*=13)	1.3±0.3*	3.0±0.6*	1.0±0.2	0.5±0.2	0.4±0.2
VHED (*N*=10)	1.5±0.3*	4.4±0.8^{+}	0.8±0.2	0.4±0.2	0.2±0.2
NED (*N*=5)	1.5±0.6*	6.2±2.7	0.7±0.2	0.5±0.2	0.3±0.2

Note. VED, vascular ED; VHED, vasculo-hormonal ED; NED – erectile dysfunction in combination with neurogenic disorders. **p*<0.01; $^{+}$*p*<0.05 in comparison with norm.

tone. Based on these reasoning, the existence of far resonances is proposed as a diagnostic sign of penile arterial deficiency.

To assess the diagnostic vista of the harmonic analysis of penile bioimpedance, we compared the harmonic parameters in healthy volunteers and in the patients with vascular, vasculo-hormonal, and neurovascular ED. For all examined groups, Figure 3 and Table 2 show the heights of M1, R1, and C1-C3 peaks. At any variant of vascular ED, all these spectrum peaks were below the norm, although the significant and rather pronounced decrease was demonstrated only by Mayer peak M1, whose mean amplitude was 3-fold smaller than the norm, and to some degree by the respiratory peak R1 (with exception of the patients with neural component of ED). The Mayer peak in spectrogram of penile bioimpedance distinguishes the healthy subjects from the patients with vascular ED (Table 2), although it cannot resolve the variants of the vascular abnormalities in ED patients with accompanied hormonal or neural disorders (Fig. 3).

The diagnostic value of penile impedance spectrometry is based on the combined documentation of the quantitative and qualitative indices. This analysis suggests the vascular disorders during ED dysfunction based on pronounced decrease in M1 and R1 peaks, on the one hand, and on the presence of stable far resonant pulsatile harmonics in the frequency range of 8-12 Hz. The existence of the near resonances of penile bioimpedance in the frequency band of 4-7 Hz is a typical feature in norm and ED, which can reflect specificity of the neural control over the tone of penile arteries. The study of this phenomenon can be useful to delineate the mechanism of ED development.

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