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Evoked Cavernous Activity: Normal Values

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Abstract

Purpose—We present normative data for evoked cavernous activity (ECA), an electrodiagnostic test that evaluates the autonomic innervation of the corpora cavernosa.

Material and Methods—We enrolled 37 healthy, sexually active and potent men for the study. Each subject completed an IIEF questionnaire and underwent simultaneous ECA and hand and foot sympathetic skin response (SSR) testing. The sympathetic skin response tests were performed as autonomic controls.

Results—Thirty six men had discernible ECA and SSRs. The mean IIEF erectile domain score was 27. ECA is a low frequency wave that is morphologically and temporally similar in both corpora. The amplitudes of the responses were highly variable. The latencies, although variable, always occurred after the hand SSR. There was no change in the quality or the latency of the ECA with age.

Conclusions—ECA is measurable in healthy, potent men in a wide range of ages. Similar to other evoked responses of the autonomic nervous system, the measured waveform is highly variable, but its presence is consistent. The association between ECA and erectile function is to be determined.

Keywords

autonomic nerve; cavernous nerve; electrodiagnostic test; penile innervation; sympathetic skin response

INTRODUCTION

In healthy men, neural impulses travel through the cavernous nerves to mediate penile vascular changes during erection and detumescence. In men with erectile dysfunction (ED) due to neurologic causes, the impairment is either in the branches of the somatic pudendal nerve, or the autonomic fibers of the cavernous nerve. In most instances of neurogenic ED, the cavernous nerve pathways are impaired; however, an accurate diagnosis is difficult without some means of assessing the extent of nerve impairment. A reliable, easy-to-use diagnostic method to accurately confirm cavernous nerve impairment would improve urologists' ability to accurately diagnose and treat neurogenic ED.

Diagnosing cavernous nerve impairment has been difficult because of problems measuring electrical activity within the corpus cavernosum. Recent advances in clinical electrophysiology

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now allow for consistent recording of intra-penile electrical activity. One promising method, called evoked cavernous activity (ECA), can be recorded following a brief, startling stimulus. The noxious stimulus results in a generalized, sympathetic nervous system discharge that manifests throughout the body, including the corpus cavernosum. When the discharge is carried through the cavernous nerves, it can be recorded in the corpora cavernosa^{1,2}. If the sympathetic innervation to the corpus cavernosum is disrupted, then ECA will not be present following the startling stimulus.

Our earlier study showed that the presence of ECA is absent in men with dysautonomias² and in most men following non-nerve sparing radical pelvic surgery, compared to a group of men after nerve sparing pelvic surgery³. We report here the results of normative ECA data, collected from a group of healthy men with intact erectile function in order to answer the following questions: 1.) What is the normal range of amplitude and latency of ECA in healthy men with intact erectile function? 2.) Is there a relationship between ECA and SSR? 3.) Is ECA similar in both corpora cavernosa? 4.) Does ECA change with age?

METHODS

The study protocol was approved by the Human Subjects Review Committee of our hospital, and a written informed consent was obtained from each subject.

Thirty seven men ages 19-68 years (mean= 38.9 years, s.d.= 16.8) were recruited from advertisements posted in our medical center and medical center website. The men were healthy and sexually active. Exclusion criteria included: moderate to severe systemic disease including, but not limited to, cardiovascular disease, obstructive pulmonary disease, autoimmune disorder, untreated hypertension, morbid obesity (body mass index >40), and neurologic disease such as stroke, neuropathy, multiple sclerosis, spinal injury or diabetes; use of medications that impair central or peripheral autonomic nerve function, particularly sympatholytics (e.g., alpha adrenergic blockers); current drug or alcohol abuse, or major psychiatric disorder; and, unwilling or unable to complete the questionnaire.

Each subject underwent a history and physical examination, with a detailed neurourological examination of the lower extremities and genitalia. Each subject completed the International Index of Erectile Function⁴.

Evoked cavernous activity (ECA) testing

With the subject supine and comfortable, a startling, but non-painful electrical stimulus was delivered to the left median nerve from a Viking IV electrophysiology machine (Viasys Healthcare, Madison, WI) via surface electrodes. The single stimulus was in the range of 5-7 milliamperes (mA), lasting approximately 0.5 msec. This brief stimulus was adequate to activate a generalized sympathetic nervous system response. ECA, which is a manifestation of the sympathetic (and therefore, autonomic) activity within the penis, was recorded from both corpora cavernosa through concentric 28 ga. needle electrodes placed into the corpora at the lateral aspect of the base of the penis. The tip of the electrode was positioned in the center of the corporal body. The recording electrodes were connected to an amplifier on the electrophysiology machine and waveforms stored for further analysis. The bandpass filters were set to low (0.2-100 Hz) frequencies. A ground plate was affixed to the skin overlying the right anterior/superior iliac crest.

The median nerve stimuli were delivered at irregular intervals of 60-120 seconds. The ECA response can fade (habituation) if the subject is drowsy, or is no longer startled by the stimulus. If ECA was reproducibly present following the first 6 stimuli, then no further stimuli were given. If ECA was not readily identifiable following all of the first 6 stimuli, then more stimuli

were delivered, up to a total of 12. The latency was measured at the first deflection from baseline following the stimulus delivery, and amplitude measurements were made peak to peak. (Figure 1.) The measurements of three of the most readily identifiable responses were averaged, for a final latency or amplitude value.

Sympathetic skin responses (SSR), which are electrophysiologic measures of dermal sympathetic activity, were measured simultaneously from the hand and foot contralateral to the median nerve stimulus. These responses were recorded as a control for the presence of a generalized sympathetic discharge. Latency and amplitude measurements of the SSRs from the hand and foot were measured in standard fashion⁵, using the values from the waveforms obtained during the same trials as the selected ECA responses.

Statistical Methods

Descriptive analysis was performed for all variables collected. Histograms were created to show the distribution of the amplitude and latency by left/right sides. Pearson correlation, visual displays, and linear regression analysis were used to study whether and how the right and left sides were correlated, as well as to study changes in amplitude and latency by age.

RESULTS

Of the 37 men enrolled in the study, 36 had discernible SSRs and ECA. One subject had SSRs that were not easily interpretable, likely due to anxiety with a resultant sustained sympathetic discharge and no discernible voltage differences in the endorgans following the stimuli. The mean IIEF erectile domain score was 27.

ECA results

Morphology—ECA is a low frequency wave, and the most notable component is a negative (upward) deflection from baseline (Figure 1). Both corpora cavernosa demonstrate simultaneous or nearly simultaneous occurrence of the ECA waveform, and both negative waves share the same, or nearly the same slope/degree of incline. In no instance did we find ECA in one corpus, but not the other. Some subjects had an ECA waveform that began with a small positive (downward) deflection, followed by a negative deflection. Occasional spontaneous discharges occurred during the ECA wave, and were shorter in duration than the ECA response (Figure 2).

Amplitude measurements—The amplitude of the responses ranged from 44-802 uV. The amplitudes of the responses from both corpora in a given subject were nearly identical, but because of habituation, level of arousal, or other factors, the amplitudes could be highly variable between trials, for a single subject. For this reason, amplitude measurements were not given much import in the final analysis. As a group, the ECA amplitudes were not normally distributed. Table 1 shows the descriptive data for the amplitude measurements, and the magnitude of the measures in the hands and foot at least an order of magnitude larger than the ECA recordings.

Latency measurements—There was a normal distribution of latency values for ECA (Figure 3). The latency of ECA responses ranged from 580 to 2873 msec on the left side and from 1193 to 2900 msec on the right side. Values observed for ECA were comparable in magnitude to the hand and foot SSRs (Table 1). In all subjects, the ECA response followed the hand SSR. This is presumably because of the longer efferent pathways from the central nervous system to the genitalia and lower extremities, as compared the efferent path to the upper extremity. In 8 subjects, ECA occurred after the onset of the foot SSR in one or both sides, and in the remaining 28 subjects, ECA occurred before the onset of the foot SSR.

Relationship between left and right sides—The Pearson correlation between the ECA in the left and right sides was .79 for amplitude and .92 for latency (both significant at .01 level) (Figure 4). For latency, the linear regression equation is $L = -97.43 + 1.04 R$, meaning that latency in the left is, on average, about 97 msec faster than the right side value. This is likely a reflection of the time differential between left and right, accounting for the fact that the stimulus is applied to the left median nerve, and the efferent response does not have to cross to the contralateral side.

Age differences—Table 2 shows the Pearson correlations between age and the measures of amplitude and latency. All correlations are not statistically different from zero (all $p > .22$). Figure 4 shows the data for latency using left and right sides. The variation of latency is about the same regardless of age. Thus, a range of normal latencies can be created to encompass all age groups.

SSR results

The latency and morphology of the hand and foot SSRs were in keeping with existing literature⁵. SSR amplitude and latency measurements are reported to be of questionable value, and the primary determinant of SSR is presence of the waveform⁶.

DISCUSSION

This is the first report of ECA recorded in healthy men with intact erectile function. It is robust and reproducible response in this group, even in men in the sixth and seventh decades of life. The ECA response is autonomically mediated, as demonstrated by its temporal association with the hand and foot SSR, slow wave morphology, habituating nature and induction of responses with a startling stimulus. As with SSR, the presence of the response is likely the most important aspect of the test, with the latency and amplitude measurements bearing less import. The similarities of latency for both right and left sides indicate that the innervation of the corpora is closely related, and is probably interconnected. Because of this interconnectedness, distinguishing the separate latencies of both the right and left sides may not be necessary for the controls. However, this may not be true in measuring neuropathological states, e.g., men following unilateral nerve sparing prostatectomies. Amplitude was too variable to be of clinical significance. The quality of the ECA response was maintained with advancing age.

We classify ECA as an autonomic response, but more specifically, it is a sympathetically-mediated event. The sympathetic response for penile function results primarily in detumescence⁷, and is not a full measure of erectile function. However, in select instances of denervation, ECA may be a reasonable surrogate measure for the parasympathetic (pro-erectile) fibers innervating the penile erectile tissue. The rationale for this is that most processes that disrupt the autonomic innervation of the penis, such as iatrogenic injury (e.g., pelvic surgery) or neuropathy, are not specific for sympathetic or parasympathetic fibers. Consequently, a technique identifying penile sympathetic denervation is likely identifying parasympathetic denervation as well. At the present time, we are limited by the lack of technology to discern neuropathy specific to pelvic parasympathetic fibers, although we do have a surrogate measure in ECA.

Developing a clinically useful measure of cavernous nerve integrity is crucial to the diagnosis and treatment of neurogenic erectile dysfunction. At this time, neurogenic ED due to cavernous nerve neuropathy (e.g., due to diabetes) or disruption (e.g., due to surgical denervation during pelvic surgery) are presumed diagnoses, because there is no direct measure of neural function. Having the ability to discriminate neurological from vascular and hormonal factors

contributing to ED would allow for a more clear understanding of the multi-faceted pathophysiology.

Yilmaz et al. examined evoked responses recorded from the penis in men with ED². They were able to measure evoked responses within the corpus cavernosum, and found these recordings more reliable and robust than the technique of corpus cavernosum electromyography (CC-EMG). CC-EMG is a measurement of spontaneous electrical activity measured within the corporal tissue, and is considered another measure of penile autonomic innervation⁸. However, there are several factors that limit the use of CC-EMG in the clinic, the most important being the difficulty in translating the waveform data to a manageable, easily interpretable form. In the Yilmaz study, the latencies of the ECA responses were easily identified and could be analyzed more readily than the highly variable and infrequent spontaneous CC-EMG activity. In addition, CC-EMG was found to be falsely absent in 16% of subjects, whereas ECA had a false negative rate of only 1.3%. Other autonomic tests associated with the evaluation of erectile dysfunction include penile skin SSR⁹ and penile skin thermal sensory analysis¹⁰. Both of these tests are at best only indirect measures of corporal tissue innervation, since the object being recorded is separate from the tissue in question.

Our findings cannot localize or define the generator that creates the evoked cavernous activity. ECA may be a measurement of electrical activity within the muscle, or it may be a measurement of smooth muscle *movement* in response to autonomic neural impulses, which would also manifest as a slow wave phenomenon. Additionally, Yarnitsky et al. did not report to know the source of the activity¹, but considered the abundant smooth muscle within the corporal tissue to be a possible generator. Thus we have chosen to use the term “activity” rather than electromyography, since we cannot know with certainty that the measurements are truly electrical activity of muscle origin.

The findings here are remarkably similar to the electrical activity measured in female erectile tissue in the clitoris and bulb. We previously described evoked bulbar activity in healthy women with no sexual dysfunction complaints¹¹. The waveform morphology of the genital responses, the range of latencies, and the relationship of the latencies to that of the hand SSR are similar between men and women. These similarities support the observation that though the gross genital anatomy is disparate between men and women, the pattern of innervation is very much alike. Further comparative studies may reveal similarities not only in innervation but in the neurophysiological responses as well¹².

Conclusions

ECA is measurable in healthy, potent men in a wide range of ages. As with other evoked responses of the autonomic nervous system, the measured waveform is highly variable, but its presence and latency measurements are consistent. As with any new test, the clinical validity of ECA needs to be tested in a range of neuropathic conditions, and the association between ECA and erectile function is to be determined.

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Key to Abbreviations

ECA	evoked cavernous activity
SSR	sympathetic skin response
ED	erectile dysfunction
CC-EMG	corpus cavernosum electromyography

Figure 1. ECA and SSR responses. A: left corpus cavernosum ECA, B: right corpus cavernosum ECA, C: hand SSR, D: foot SSR. Stimulus is delivered at time zero, designated by the vertical line on the left of the figure. Latency is measured from onset of the stimulus to the start of the response. Amplitude is measured from peak to peak. ECA responses from both corpora are similar in morphology and latency. It is temporally related to the SSR responses from the hand and foot, supporting its autonomic nature. ECA = evoked cavernous activity, SSR = sympathetic skin response, L = latency, a = amplitude. Time base 1 sec/div., amplitudes noted on figure.

Figure 2.

Demonstration of spontaneous corporal activity (spikes) occurring between 5 and 6 seconds. It occurs in both corpora, is not simultaneous, and does not appear in the SSRs. A: left corpus cavernosum ECA, B: right corpus cavernosum ECA, C: hand SSR, D: foot SSR. ECA = evoked cavernous activity, SSR = sympathetic skin response. Time base 1 sec/div., amplitudes noted on figure.

Figure 3.
Histograms for ECA latency distributions.

Figure 4.

Relationship between left and right ECA latency. The left ECA latency is, on average, about 97 msec faster than the right side value. This is likely a reflection of the time difference for stimulus from the left median nerve to cross to the right side.

Table 1

Descriptive Data

Measure	Mean (Standard deviation)	Median (Range)
Amplitude (uV)		
Right ECA	284.0 (166.0)	260.8 (46.3-726.7)
Left ECA	301.7 (205.2)	231.7 (44.7-802.0)
Hand SSR	3017.8 (1549.7)	2796.3 (379.7-6923.0)
Foot SSR	2122.5 (1439.5)	1854.7 (248.0-7337.0)
Latency (msec)		
Right ECA	1883.9 (410.2)	1846.7 (1193.3-2900.0)
Left ECA	1866.3 (466.4)	1840.0 (580.0-2873.3)
Hand SSR	1628.7 (213.7)	1626.7 (1193.3-2153.3)
Foot SSR	2254.2 (297.2)	2330.0 (1426.7-2793.3)

Table 2

Correlations between age and measures of amplitude and latency. There is no significant change in latency or amplitude with advancing age.

Measure	Correlation with Age	P-value *
Amplitude		
Right ECA	-.18	.29
Left ECA	-.21	.22
Latency		
Right ECA	.04	.83
Left ECA	.06	.64

* P-value for the test of hypothesis that the correlation is zero = no linear association