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Short Communication

Nocturnal penile erections: A retrospective study of the role of RigiScan in predicting the response to sildenafil in erectile dysfunction patients

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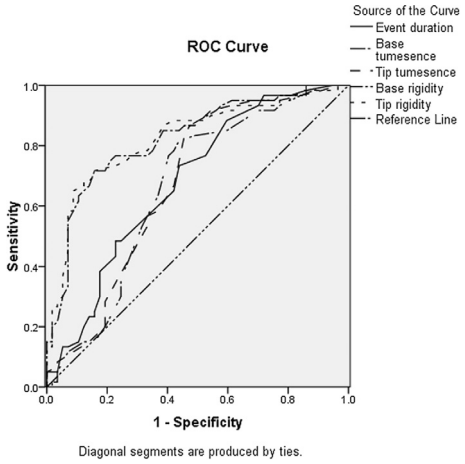
GRAPHICAL ABSTRACT



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ABSTRACT

Sildenafil enhances the nitric oxide–cGMP pathway of erection, which is claimed to have a role in nocturnal penile tumescence and rigidity (NPTR). This study aimed to find whether RigiScan can predict the response to sildenafil among erectile dysfunction (ED) patients and to find which RigiScan parameter produces the best prediction. Medical records of 172 ED patients were revised regarding their full sexual history, standard andrology examination, NPTR monitoring by the RigiScan device, and the degree of response to sildenafil. Of 172 ED patients, 94 patients (54.7%) were sildenafil responders. All RigiScan parameters were higher in the sildenafil responder group. The RigiScan parameters with the most differentiating power between both sildenafil responders and non-responders were base rigidity (AUC 0.860) and then tip rigidity (AUC 0.831). The cut-off value of base and tip rigidity with the highest diagnostic accuracy was 42.5%. This finding was found to be more specific than the sensitivity in predicting a positive response to sildenafil (85.9% *vs.* 70.2% and 92.3% *vs.* 59.6%, for base and tip rigidity, respectively). Sildenafil response in ED cases can be predicted through NPTR monitoring using the RigiScan device and ED patients with RigiScan base or tip rigidity less than 42% are not expected to respond well to sildenafil.

Introduction

Since Bradley introduced the RigiScan device in 1985 as a tool to monitor nocturnal penile tumescence and rigidity (NPTR) [1], it has

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been used extensively as a diagnostic and research tool for evaluation of penile erections. However, based on the findings of the published data, the accuracy, the reliability and usefulness of RigiScan are still controversial. The greatest value of NPTR is for the patient with no neurovascular risk factors, who presents with a sexual history suggestive of a psychogenic cause [2]. Researchers used RigiScan not only to differentiate between psychogenic and organic causes of ED [1,3–5], but also to detect whether RigiScan could determine the underlying ED organic causes [6] and to assess ED severity [7]. RigiScan was used also to evaluate the penile response to different ED treatments [8–11].

Nocturnal penile erection was reported to occur in all men of different age groups during periods of rapid eye movement (REM) sleep [12]. It was assumed that during sleep psychological factors cannot interfere with nocturnal erection, whereas organic factors can interfere variously. Therefore, evaluation of NPTR can differentiate between psychogenic and organic causes of ED. During sexual stimulation, nitric oxide (NO), the major vasodilator neurotransmitter involved in the erection pathway, is released in response to central and local erectogenic stimuli from the intracavernosal endothelial cells and the autonomic nervous system. It then induces formation of cyclic guanosine monophosphate (cGMP), which induces cavernosal smooth muscle relaxation; hence, erection occurs [13]. How nocturnal erections are induced is still unknown, but NO was found to be released during REM sleep [14], and then the cascade of erection events was completed.

Since the introduction of sildenafil as the first FDA-approved PDE-5 inhibitor oral drug for ED treatment, PDE-5 inhibitors were considered the first line in ED correction [15]. However, oral sildenafil did not give satisfactory results in all cases of ED [16]. It is beneficial for andrologists and ED patients to predict the response to sildenafil, because this will improve its cost effectiveness and help to avoid its unnecessary side-effects [17]. Many studies were conducted to detect which parameters could predict the response to sildenafil, varying from the simple, non-invasive morphometric parameters up to the invasive ones such as cavernosometry and even penile biopsy [16,18,19]. However, it was found that some clinical measures, such as the ED duration and the international index of erectile function-5 (IIEF-5) score, could predict such response [20]. Sildenafil performs its pharmacologic action through inhibition of the PDE-5 iso-enzyme and thus enhances the NO–cGMP pathway of erection [21]. This cGMP pathway is claimed to be involved in NPTR [14], so cGMP is a common key factor between sildenafil and NPTR, and this finding suggests that NPTR monitoring by the RigiScan device may be able to predict the sildenafil response in ED patients.

This study aimed to assess whether RigiScan can predict the response to sildenafil in ED patients and to determine which of the RigiScan parameters can best perform this prediction.

Patient and methods

Data for this study were retrospectively extracted from the medical records of 172 ED patients who attended Mansoura University Andrology Outpatient clinics and three private andrology clinics during the period from January 2010 to May 2017. Selected cases should have had ED for more than 6 months with regular (at least once per week) heterosexual relations with one partner.

Approval of the local ethical committee was obtained before the study. We included only the cases that met the inclusion criteria and who had complete records regarding the following: full sexual history, standard andrology examination, measurement of postprandial blood sugar, serum prolactin and total testosterone levels, NPTR monitoring and those given sildenafil in an optimum way as described below.

NPTR monitoring

NPTR monitoring was performed for 3 successive nights in a sleep unit, using the RigiScan device (Osbon Medical Systems; Augusta, GA, USA). Instructions were given to ensure restful sleep by avoidance of napping, alcohol and caffeine intake, and evacuation of the bladder and bowel before going to sleep. Data were obtained each morning with recording of tip and base tumescence, tip and base rigidity, and duration of the single best event in the 3 nights.

Sildenafil administration

Patients with penile anatomic disorders, severe uncontrolled medical diseases or in whom sildenafil is contraindicated were not given sildenafil in all of our records. Sildenafil was first given in a dose of 50 mg 1 h before intercourse on an empty stomach. Patients were asked to record their penile erectile response using the Erection Hardness Scale (EHS) [22]. The dose was escalated to 100 mg if the responses to 6 initial doses were insufficient, i.e., EHS grade 1 or 2. After 6 consecutive doses of 100 mg sildenafil, patients were classified, according to their response to sildenafil, into 2 groups: sildenafil responders (EHS grade 3 or 4) and sildenafil non-responders (EHS grade 1 or 2).

Statistical analysis

A test for normal distribution (Kolmogorov–Smirnov test) was carried out first for all studied variants. Differences between sildenafil responders and non-responders were studied by the independent sample Student's *t*-test for parametric variants and Mann-Whitney test for non-parametric variants. The receiver operator characteristic (ROC) curve was performed for all RigiScan parameters to determine their area under the curve (AUC) and their cut-off values that had the highest diagnostic accuracy.

Results

This study included 172 ED patients. Ninety-four patients were sildenafil responders (54.7%), whereas 78 patients were sildenafil non-responders (45.3%).

Different RigiScan parameters of the best NPTR event, i.e. event duration, both base and tip tumescence and both base and tip rigidity, were higher in the sildenafil responders than in the sildenafil non-responders, with statistical significance (Table 1).

RigiScan parameters of the best NPTR event in all patients showed significant positive correlation between each other (r ranged between 0.23 and 0.93, and *P* ranged between 0.001 and 0.003).

Table 1
RigiScan parameters in both sildenafil responders and non-responders.

	Sildenafil responders (n = 94)	Sildenafil non-responders (n = 78)	*P* value
Event duration (min)	17.2 ± 8.6	13 ± 6.8	0.001[b]
Base tumescence (cm)	3.1 ± 0.5	2.6 ± 0.7	0.001[a]
Tip tumescence (cm)	2.2 ± 0.4	1.8 ± 0.5	0.001[b]
Base rigidity (%)	49.7 ± 10.9	33.4 ± 9.7	0.001[a]
Tip rigidity (%)	44.8 ± 11.6	30 ± 9.8	0.001[a]

[a] Independent sample *t*-test.
[b] Mann-Whitney test.

Table 2
ROC curve analysis and area under the curve (95% confidence interval) of different RigiScan parameters as differentiating items between sildenafil responders and non-responders.

	AUC	95% Confidence interval	
		Lower bound	Upper bound
Event duration	0.674	0.598	0.761
Base tumescence	0.722	0.642	0.802
Tip tumescence	0.718	0.637	0.798
Base rigidity	0.860	0.807	0.913
Tip rigidity	0.831	0.773	0.890

By obtaining the ROC curve and its AUC as an indicator of diagnostic accuracy, it was found that event duration had the lowest AUC (0.674), whereas base rigidity had the highest AUC (0.86) (Table 2, Fig. 1).

The cut-off values of different RigiScan parameters were determined by the point of the ROC curve with the highest diagnostic accuracy. Diagnostic accuracy was the lowest for the best event duration (68%), and it was the highest for base rigidity (77.3%), followed by tip rigidity (74.4%) as a single predicting parameter. While using the cut-off values of different RigiScan parameters in predicting sildenafil response, we found statistically that a positive response to sildenafil is best predicted if either base rigidity or tip rigidity is ≥42.5% with a diagnostic accuracy of 76.7% (Table 3).

The cut-off value (42.5%), when used separately for base rigidity and then for tip rigidity, was found to be more specific than sensitive (85.9% *vs.* 70.2% and 92.3% *vs.* 59.6%, respectively). However, if the same cut-off value (42.5%) was used for both base rigidity and tip rigidity together as a single unit, its specificity increased to 94.9% and its sensitivity decreased to 58.5% (Table 3).

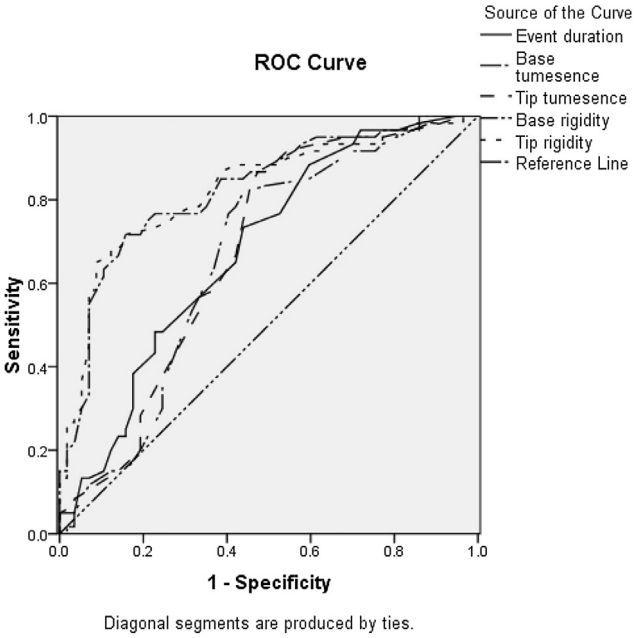

Fig. 1. ROC curve analysis and AUC of different RigiScan parameters as an indicator of diagnostic accuracy.

Discussion

Sildenafil citrate, which is one of the most widely used oral drugs for ED, performs its pharmacologic action through inhibition of the PDE-5 iso-enzyme and thus enhances the NO–cGMP pathway of erection [21]. This pathway is claimed to be involved in NPTR [14]. Therefore, two questions will be raised here. The first question is what the effect of sildenafil is on NPTR. The second question is whether NPTR monitoring can predict the response to sildenafil in ED patients.

In answer to the first question, many studies were conducted to test the effect of sildenafil on NPTR in different patient groups. A study by Montorsi et al. showed that the number of RigiScan NPTR episodes increased after intake of sildenafil, but the recorded values did not reach statistical significance [23]. On the other hand, many researchers found a beneficial effect of sildenafil on almost all NPTR parameters in different patient groups, such as in cases of psychogenic ED not responding to sildenafil during awakening [8], in cases with organic ED [24] and even in healthy, potent volunteers [11]. Initially, PDE-5 inhibitors were used widely with the primary intention of compensating for a symptom rather than to correct the underlying pathophysiology in both psychogenic and organic ED. In recent years, several investigations have addressed the potential for disease modification or cure via long-term PDE-5 inhibitor therapy. There are data supporting a potential role for daily PDE-5 inhibitor administration in improving both psychogenic and organic ED [25]. However, for answering the second question, no study has been conducted to date to assess whether RigiScan can predict sildenafil response.

In this study, patients were considered to be sildenafil responders if they could get an erection with hardness (rigidity) sufficient for sexual intercourse or fully rigid erection, that is, EHS grade 3 or 4. A previous study revealed that EHS has a positive correlation with the international index of erectile function-erectile domain (IIEF-EF), frequency of erections hard enough for penetration and hence successful sexual intercourse [26]. All parameters of NPTR as monitored by RigiScan showed lower values in sildenafil non-responders than in the responder group. The physiologic role of NPTR is an issue that is still not completely determined, but NPTR may act to maintain oxygenation of erectile tissue, which is important to maintain a normal erectile response [27], especially in the absence of frequent sexual stimulation. Oxygen (O_2) is essential for synthesis of NO, and a low oxygen state inhibits nitric oxide synthase (NOS) [24]. The corpora cavernosa contains both smooth muscle and connective tissue content. An adequate balance between them is essential for competent veno-occlusion [27]. Cavernous hypoxia promotes formation of transforming growth factor beta (TGFβ) that increases collagen synthesis with resultant cavernous fibrosis [28]. Therefore, regular increase in blood flow dur-

Table 3
Cut-off values of different RigiScan parameters and their diagnostic indicators when comparing sildenafil responders and non-responders.

	Cut-off values	Sensitivity (n = 94)	Specificity (n = 78)	Diagnostic accuracy (n = 172)
Event duration	11.5	80.9%	52.6%	68%
Base tumescence	2.75	76.6%	67.9%	72.7%
Tip tumescence	1.75	83%	60.3%	72.7%
Base rigidity	42.5	70.2%	85.9%	77.3%
Tip rigidity	42.5	59.6%	92.3%	74.4%
Base rigidity + tip rigidity	42.5	58.5%	94.9%	75%
Base rigidity or tip rigidity	42.5	71.3%	83.3%	76.7%

ing erection might hinder conversion of erectile tissue to a fibrous one. ED patients showed lower O_2 saturation of corporal tissue in the flaccid state than did potent cases. Many cases not responding to sildenafil therapy showed severe vascular lesion with reduction of their cavernosal smooth muscle cell O_2 content [19]. Administration of corporal vasoactive material caused a many-fold increase in O_2 saturation [29]. Also, some cases with sleep apnoea and ED with no nocturnal penile activity showed improved erectile function and restoration of NPTR when treated with continuous positive airway pressure treatment [30].

All RigiScan parameters were retested by the ROC curve analysis to detect which of them was the best in predicting the response to sildenafil. Base rigidity and then tip rigidity were found to be associated with the highest area under the curve (AUC about 0.860, 0.831, respectively) with the highest diagnostic accuracy (77.3% and 74.4%, respectively). The cut-off value for both base rigidity and tip rigidity was about 42.5%. On trying to use both base rigidity and tip rigidity together in predicting the response to sildenafil, the diagnostic accuracy did not significantly change. This can be explained by our finding of the high positive correlation between different RigiScan parameters; thus, one parameter amongst them can express their altogether state. However, an interesting finding is that the cut-off values of both base rigidity and tip rigidity were more specific than sensitive (85.9% *vs.* 70.2% and 92.3% *vs.* 59.6%, respectively); that is, our prediction model is more accurate in excluding cases with negative response than in detecting cases with positive response to sildenafil. This exclusion power is heightened to 94.9% when the patient has either a base rigidity or a tip rigidity of <42.5%.

Conclusions

From these findings, it can be concluded that sildenafil response in ED patients can be predicted by NPTR monitoring, using the RigiScan device, and ED patients with a RigiScan base or tip rigidity less than 42% cannot be expected to respond well to sildenafil.

Conflict of interest

The authors have declared no conflict of interest.

References

[1] Bradley W, Timm G, Gallagher J, Johnson B. New method for continuous measurement of nocturnal penile tumescence and rigidity. Urology 1985;26:4–9.

[2] Jannini Emmanuele A, Granata Antonio M, Hatzimouratidio Konstantinos, Goldstein Irwin. Use and abuse of RigiScan in the diagnosis of eractile dysfunction. J Sex Med 2009;6:1820–9.

[3] Bella AJ, Lee JC, Carrier S, Bénard F, Brock GB. 2015 CUA Practice guidelines for erectile dysfunction. Can Urol Assoc J 2015;9:23–9.

[4] Hatzichristou D, Hatzimouratidis K, Ioannides E, Yannakoyorgos K, Dimitriadis G, Kalinderis A. Nocturnal penile tumescence and rigidity monitoring in young potent volunteers: reproducibility, evaluation criteria and the effect of sexual intercourse. J Urol 1998;159:1921–6.

[5] Hatzichristou D, Rosen RC, Derogatis LR, Low WY, Meuleman EJ, Sadovsky R, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337–48.

[6] Elhanbly S, Elkholy A. Nocturnal penile erections: the role of RigiScan in the diagnosis of vascular erectile dysfunction. J Sex Med 2012;9:3219–26.

[7] Yang CC, Porter MP, Penson DF. Comparison of the International Index of Erectile Function erectile domain scores and nocturnal penile tumescence and rigidity measurements: does one predict the other? BJU Int 2006;98:105–9. discussion 109.

[8] Abdel-Naser MB, Imam A, Wollina U. Sildenafil citrate significantly improves nocturnal penile erections in sildenafil non-responding patients with psychogenic erectile dysfunction. Int J Impot Res 2004;16:552–6.

[9] Diamond LE, Earle DC, Garcia WD, Spana C. Co-administration of low doses of intranasal PT-141, a melanocortin receptor agonist, and sildenafil to men with erectile dysfunction results in an enhanced erectile response. Urology 2005;65:755–9.

[10] Hellstrom WJ, Freier MT, Serefoglu EC, Lewis RW, DiDonato K, Peterson CA. A phase II, single-blind, randomized, crossover evaluation of the safety and efficacy of avanafil using visual sexual stimulation in patients with mild to moderate erectile dysfunction. BJU Int 2013;111:137–47.

[11] Yaman O, Tokatli Z, Akand M, Elhan AH, Anafarta K. Characteristics of sildenafil erections in healthy young men. Asian J Androl 2005;7:395–8.

[12] Karacan I, Williams RL, Thornby JI, Salis PJ. Sleep-related penile tumescence as a function of age. Am J Psychiatry 1975;132:932–7.

[13] Greenstein A, Chen J, Salonia A, Sofer M, Matzkin H, Montorsi F. Does sildenafil enhance quality of nocturnal erections in healthy young men? A NPT-RigiScan study. J Sex Med 2004;1:314–7.

[14] Burnett AL. Nitric oxide in the penis: physiology and pathology. J Urol 1997;157:320–4.

[15] Nehra A, Colreavy F, Khandheria BK, Chandrasekaran K. Sildenafil citrate, a selective phosphodiesterase type 5 inhibitor: urologic and cardiovascular implications. World J Urol 2001;19:40–5.

[16] Huang ST, Hsieh ML. Different hemodynamic responses by color Doppler ultrasonography studies between sildenafil non-responders and responders. Asian J Androl 2007;9:129–33.

[17] Chia SJ, Ramesh K, Earnest A. Clinical application of prognostic factors for patients with organic causes of erectile dysfunction on 100 mg of sildenafil citrate. Int J Urol 2004;11:1104–9.

[18] Padma-Nathan H. Sildenafil citrate (Viagra) treatment for erectile dysfunction: An updated profile of response and effectiveness. Int J Impot Res 2006;18:423–31.

[19] Wespes E, Rammal A, Garbar C. Sildenafil non-responders: haemodynamic and morphometric studies. Eur Urol 2005;48:136–9. discussion 139.

[20] Elhanbly S, Elkholy AA, Alghobary M, Abou Al-Ghar M. Clinical predictive factors of sildenafil response: a penile hemodynamic study. Andrology 2015;3:241–6.

[21] Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. Int J Impot Res 1996;8:47–52.

[22] Boolell M, Gepi-Attee S, Gingell JC, Allen MJ. Sildenafil, a novel effective oral therapy for male erectile dysfunction. Br J Urol 1996;78:257–61.

[23] Montorsi F, Maga T, Strambi LF, Salonia A, Barbieri L, Scattoni V, et al. Sildenafil taken at bedtime significantly increases nocturnal erections: results of a placebo-controlled study. Urology 2000;56:906–11.

[24] Terradas C, Levalle O, Nagelberg A, Mormandi E. Sildenafil improves nocturnal penile erections in organic impotence. Int J Impot Res 2001;13:125–9.

[25] Ferdinando F, Elisa R, Ciro I, Andrea R, Paolo V, Vincenzo M. A new era in the treatment of erectile dysfunction chronic: phosphodiestrase type 5 inhibition. BJU Int 2010;105:1634–9.

[26] Mulhall JP, Levine LA. Jünemann KP Erection hardness: a unifying factor for defining response in the treatment of erectile dysfunction. Urology 2006;68:17–25.

[27] Nehra A, Goldstein I, Pabby A, Nugent M, Huang YH, de las Morenas A,, et al. Mechanisms of venous leakage: a prospective clinicopathological correlation of corporeal function and structure. J Urol 1996;156:1320–9.

[28] Ryu JK, Song SU, Choi HK, Seong DH, Yoon SM, Kim SJ, et al. Plasma transforming growth factor-beta1 levels in patients with erectile dysfunction. Asian J Androl 2004;6:349–53.

[29] Padmanabhan P, McCullough AR. Penile oxygen saturation in the flaccid and erect penis in men with and without erectile dysfunction. J Androl 2007;28:223–8.

[30] Karacan I, Karatas M. Erectile dysfunction in sleep apnea and response to CPAP. J Sex Marital Ther 1995;21:239–47.