"Contemporary Management of Post-Prostatectomy Sexual Dysfunction: From Penile Rehabilitation Toward a Global Sexual Assessment"

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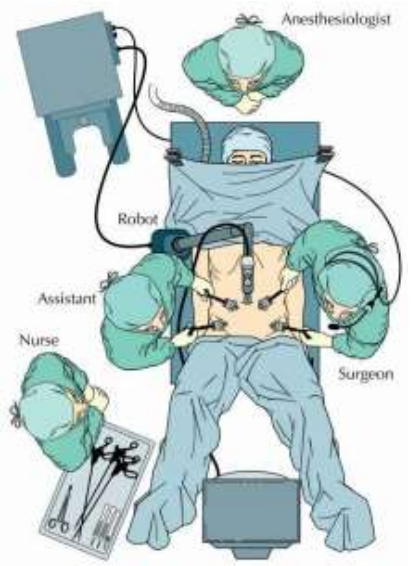
PCa / Radical Prostatectomy

- **PCa is one of the most frequent cancers in men**
  - second most commonly diagnosed *(EAU Guidelines 2017)*
  - an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed
- **Health Campaigns**
  - PCa is usually diagnosed promptly
  - Localized within the prostate gland
- **Radical Prostatectomy**
  - One of the gold standards of treatment:
    - Open
    - Laparoscopic
    - Robot-Assisted Laparoscopic

- **Sexual Dysfunction…**

Sexual Dysfunction - RP

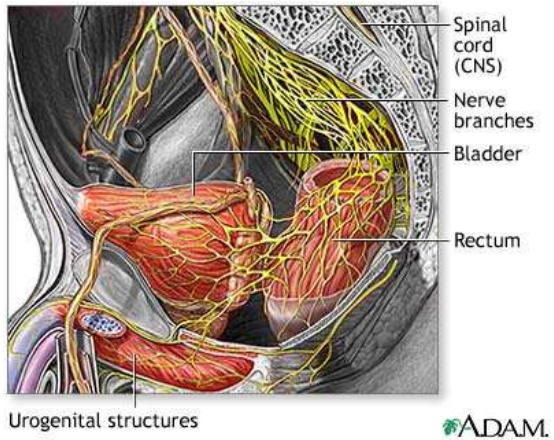
- **Erectile Dysfunction (ED)**
  - Most studied
  - Incidence: 6% - 68% (Ficarra et al. Eur Urol 2012; 62: 418)
- **True Anejaculation (Aspermia) (anatomo-physiology)**
- **Libido Disorders**
- **Urinary Incontinence at the Time of Orgasm (Climacturia)**
- **Orgasmic Disturbances**
  - Altered perception of orgasm
  - Anorgasmia
  - Orgasm-associated pain **(dysorgasmia)**
- **Penile Shortening**
- **"De Novo" Deformity (Curvature – Peyronie's)**

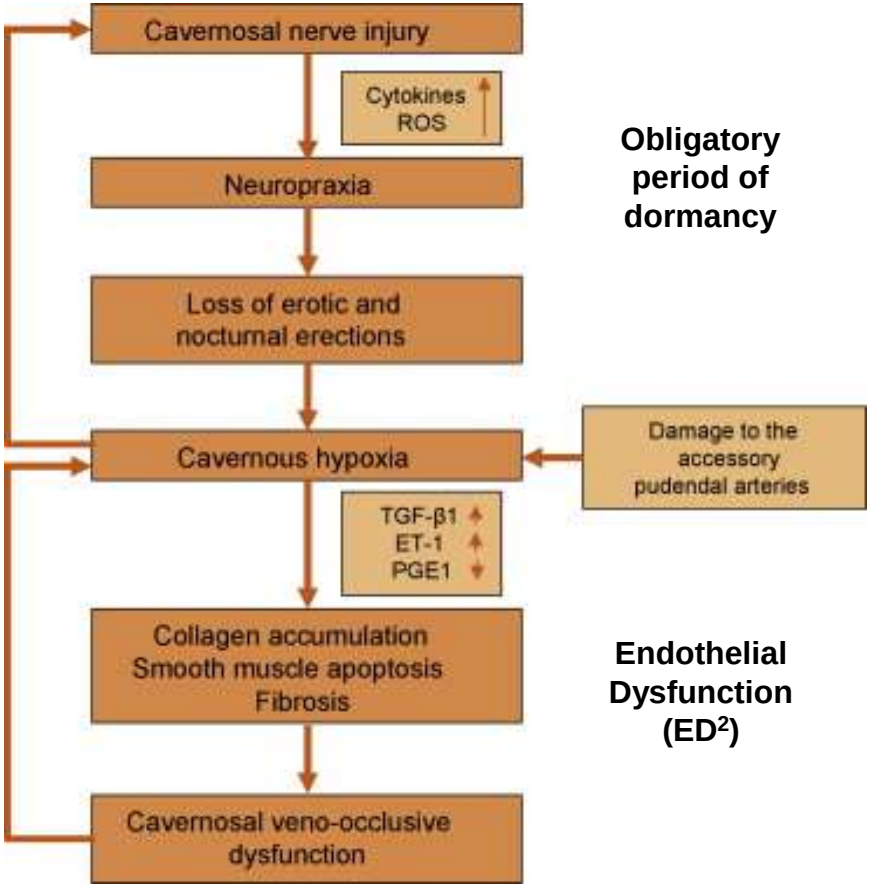


Fode et al. Sex Med Rev 2017, 5: 110

ED - Pathophysiology

- **Neurovascular Bundle Trauma**
  - Mechanical manipulation
  - Heating
  - Ischemic effects
  - Local inflammation
- **Neurogenic ED**
  - Reversible / Irreversible





Hatzimouratidis et al.
Eur Urol 2008, 2: 334

ED - Pathophysiology

HISTOLOGICAL ALTERATIONS IN CAVERNOUS TISSUE AFTER RADICAL PROSTATECTOMY

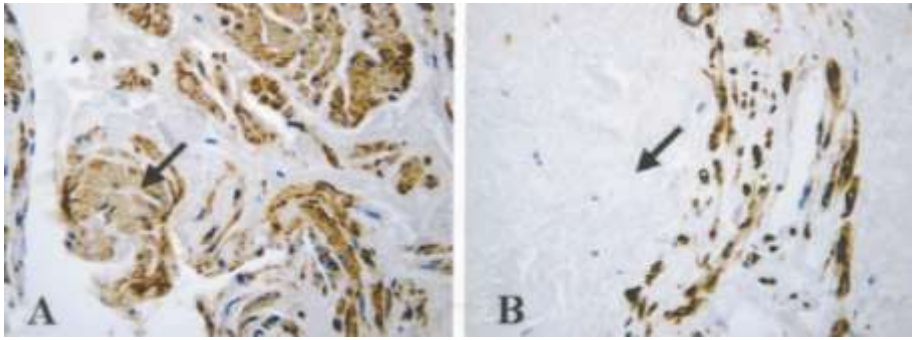
FABRIZIO IACONO, RENATO GIANNELLA, PASQUALE SOMMA, GIUSEPPE MANNO, FERDINANDO FUSCO AND VINCENZO MIRONE

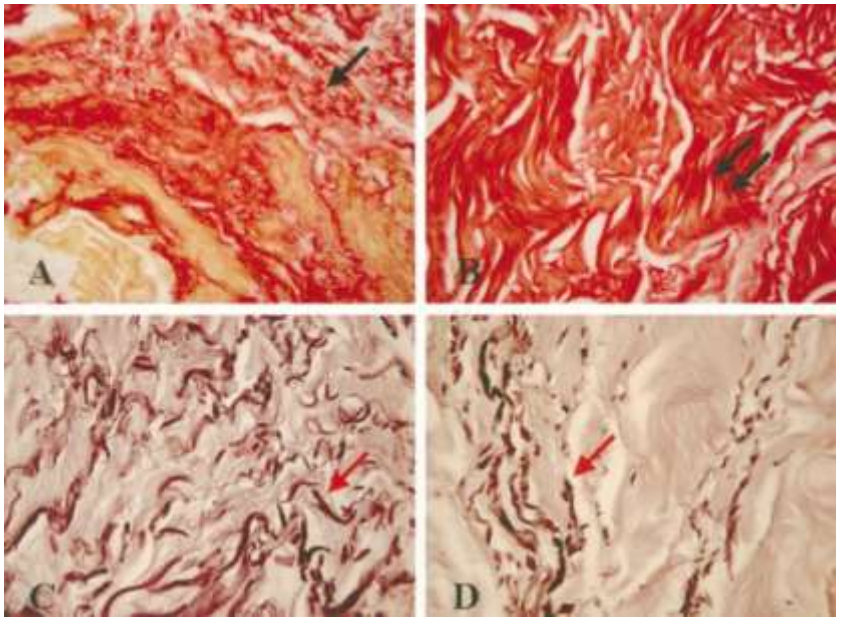
Vol. 173, 1673–1676, May 2005

Elastic and collagen fibers in 19 patients before, and 2 and 12 months after radical prostatectomy

	Mean Fibers ± SD	
	Elastic/High Power Field	Collagen/% Biopsy Area
Before	129.32 ± 13.13	44.80 ± 5.73
After 2 mos	80.80 ± 23.26	55.05 ± 5.29
After 12 mos	44.20 ± 11.58	73.10 ± 7.85

Before vs after 2 and 12 months, and after 2 vs 12 months $p < 0.0003$.



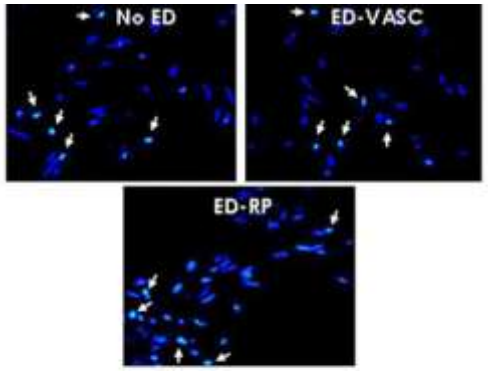


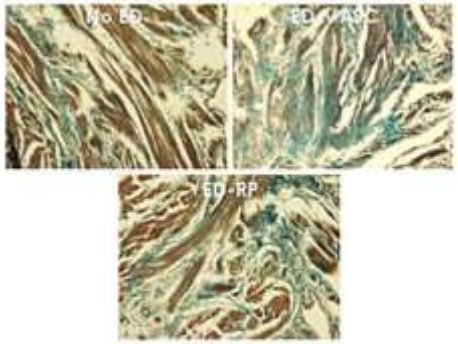
ED - Pathophysiology

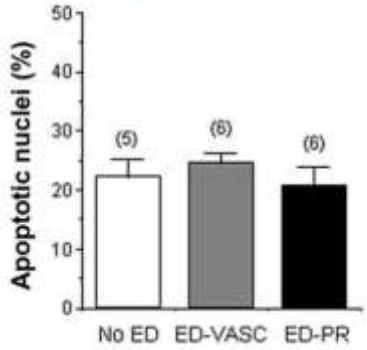
Nitrergic Function Is Lost but Endothelial Function Is Preserved in the Corpus Cavernosum and Penile Resistance Arteries of Men after Radical Prostatectomy

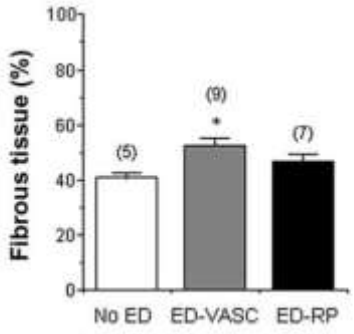
J Sex Med 2015;12:590–599.

Juan I. Martínez-Salamanca, MD, PhD,* José M. La Fuente, MD, PhD,† Argentina Fernández, LT,‡ Eduardo Martínez-Salamanca, LT,‡ Augusto J. Pepe-Cardoso, MD,§ Joaquín Carballido, MD, PhD,* and Javier Angulo, PhD‡









- **Marked Imbalance in neurogenic modulation of cavernosal tone**
- **In favor of adrenergic contractile responses over nitrergic relaxation**
  - **Because endothelial function sensitivity to PDE5-Is may be preserved**
  - **Accounting for penile shortening over time…**

ED/RP – General Guidelines

- **Postoperative recovery of erectile function**
  - **Chronological aspects are important**
    - **Recovery can occur years following RP (up to 48 months)**
  - **It is shared opinion that the timing of any kind of therapy should be commenced as close as possible to the surgical procedure**
  - **Rehabilitation and treatment are undoubtedly better than leaving the erectile tissue to its unassisted, unfavorable fate**
  - **Use of pro-erectile drugs following RP is important in achieving postoperative erectile function**
  - **What about Penile/Sexual Rehabilitation?**
    - **If so, when should we stop?**

Glickman et al. J Urol 2009, 181: 731
Salonia et al. Eur Urol, 2012, 62: 273

ED - Pathophysiology

INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2016) 23, 614–622 doi: 10.1111/iju.13105

Original Article: Laboratory investigation

Penile erection induces angiogenic, survival, and antifibrotic signals: molecular events associated with penile erection induced by cavernous nerve stimulation in mice

Mi-Hye Kwon,[1,†] Soo-Hwan Park,[1,†] Kang-Moon Song,[1] Kalyan Ghatak,[1] Anita Limanjaya,[1] Dong-Soo Ryu,[2] Jiyeon Ock,[1] Soon-Sun Hong,[3,4] Ji-Kan Ryu[1,4] and Jun-Kyu Suh[1]

[1]National Research Center for Sexual Medicine and Department of Urology, Inha University School of Medicine, Incheon, [2]Department of Urology, Sungkyunkwan University School of Medicine, Samsung Changwon Hospital, Changwon, [3]Department of Medicine, and [4]Inha Research Institute for Medical Sciences, Inha University School of Medicine, Incheon, Korea

- ***Objectives:***

To determine the molecular events related to penile erection in the corpus cavernosum tissue of mice after electrical stimulation of the cavernous nerve.

- ***Conclusions:***

Penile erection in mice is accompanied by the activation of a cascade of signaling pathways involved in angiogenesis, cell survival and proliferation, and antifibrosis. The present results might provide a theoretical and molecular basis for understanding the importance of penile rehabilitation and subsequent restoration of nocturnal or sexually-mediated penile erections.

ED - Pathophysiology

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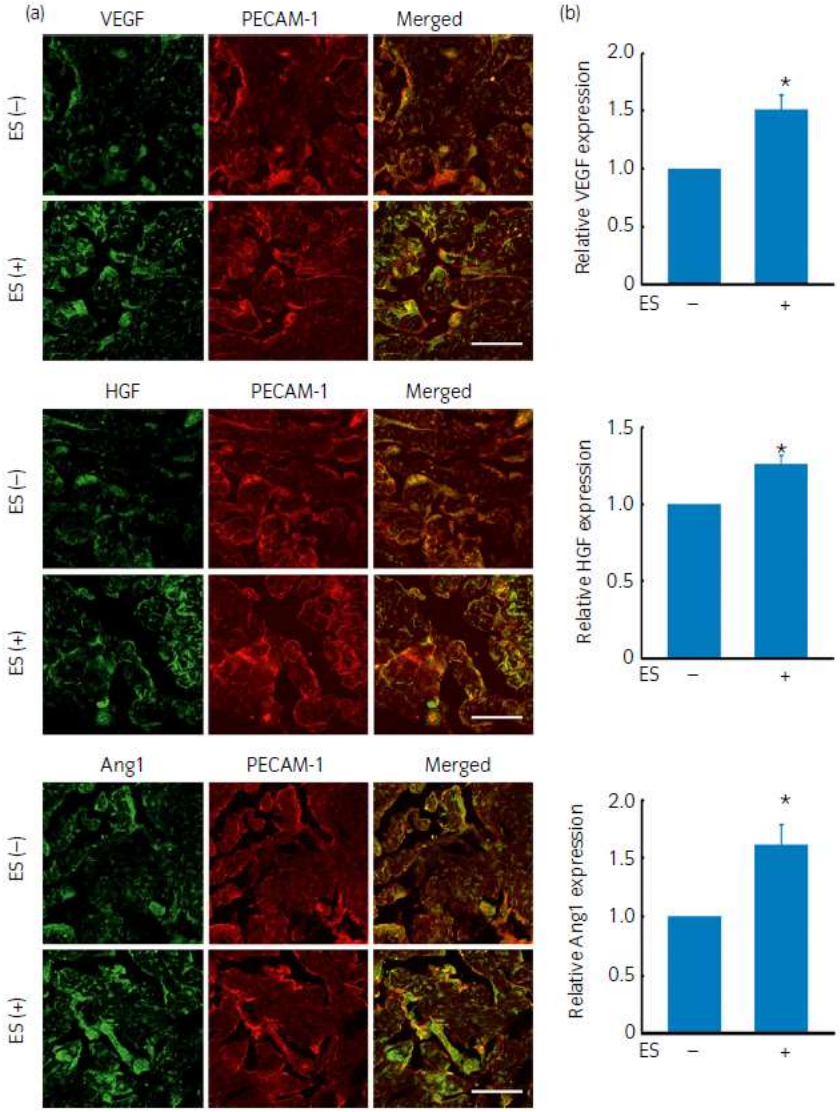
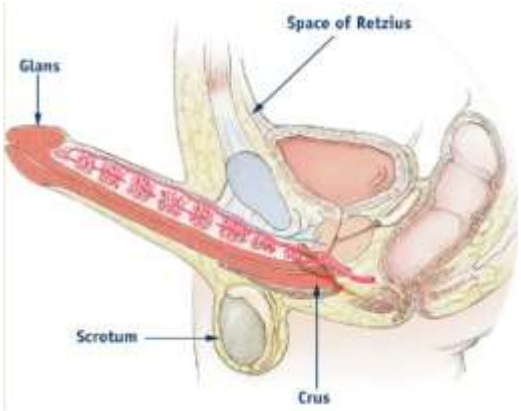
Higher expression of VEGF, HGF and Ang1 in the corpus cavernosum tissue of mice that received ES of the cavernous nerve than in unstimulated controls

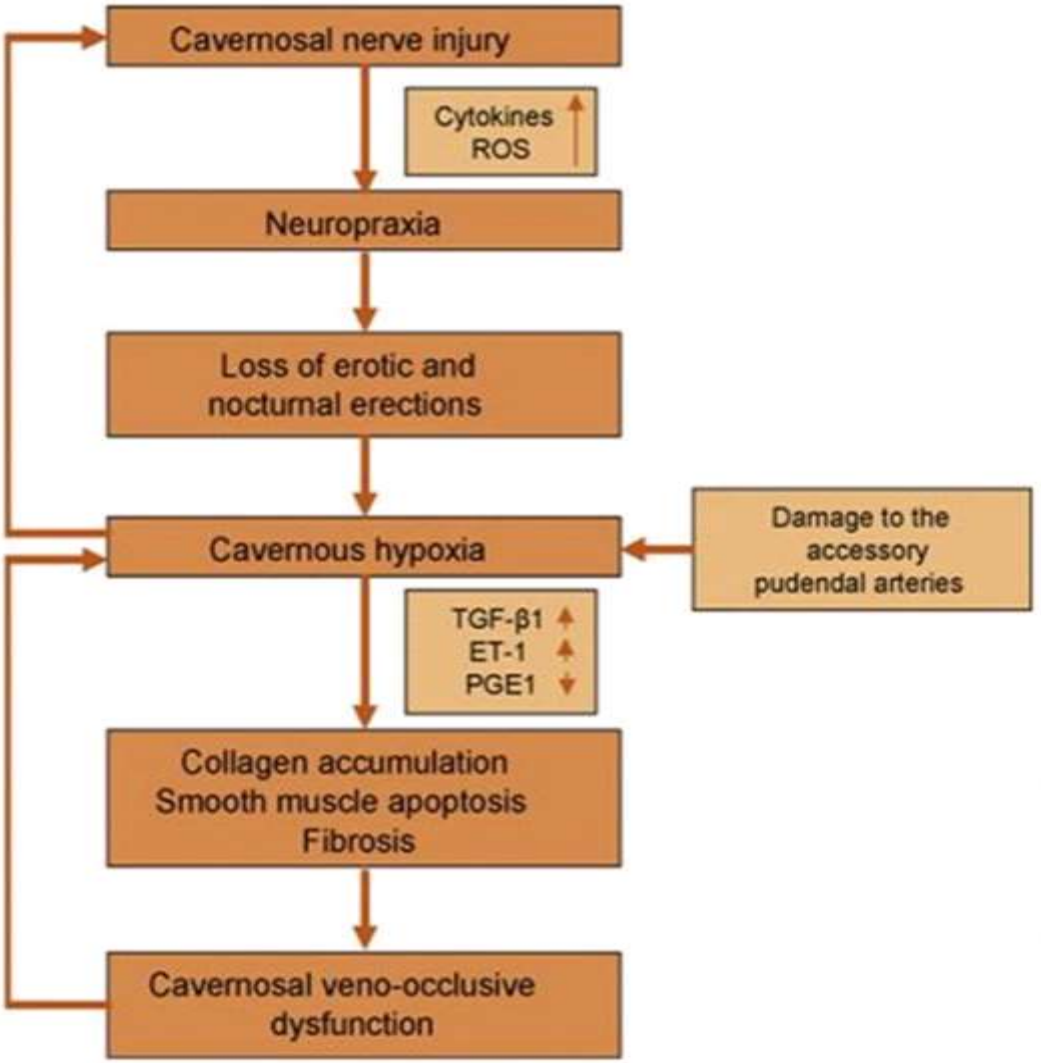


Sexual Dysfunction - RP

Penile rehabilitation, The idea that one can improve the long term spontaneous erectile function through early and continous treatment of ED immediatly following radical prostatectomies



ED after nerve-sparing RP



Hatzimouratidis et al.
Eur Urol 2008, 2: 334

Levels of evidence

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected Authorities

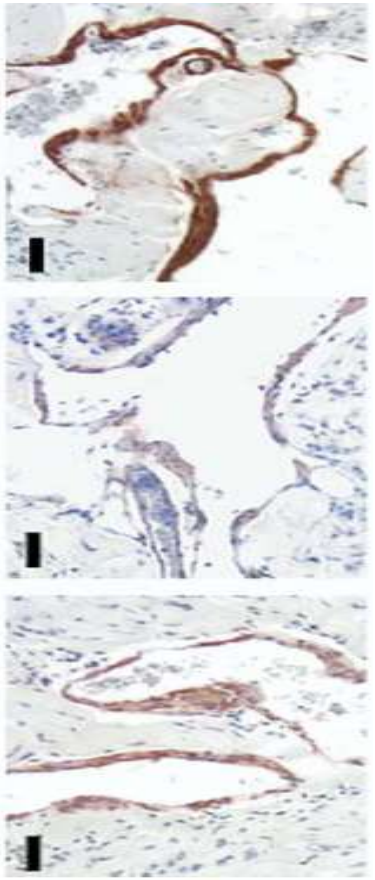
PDE5-inhibitors in penile rehabilitation

- On-demand PDE-5 inhibitors
- Daily PDE-5 inhibitors
  - Sildenafil
  - Vardenafil
  - Tadalafil
  - Avanafil

PDE5-I after nerve damage in Rats

- **Benefits**
  - ↑ cavernosal pressure after injection or electrical stimulation
  - ↑smooth muscle
  - ↓fibrosis

- **Possible mechanisms**
  - cGMP and NO activation
  - Hypoxia
  - Endothelial protection
  - Anti-apoptotic and anti-fibrotic factors
  - Oxidative stress
  - Increased cell proliferation
  - Nerve protection



Klein et al, J Urol 1997; Vignozzi et al, Int J Impot Res. 2008; Mulhall et al, J Sex Med. 2008; Kovanecz et al, Int J Impot Res. 2008

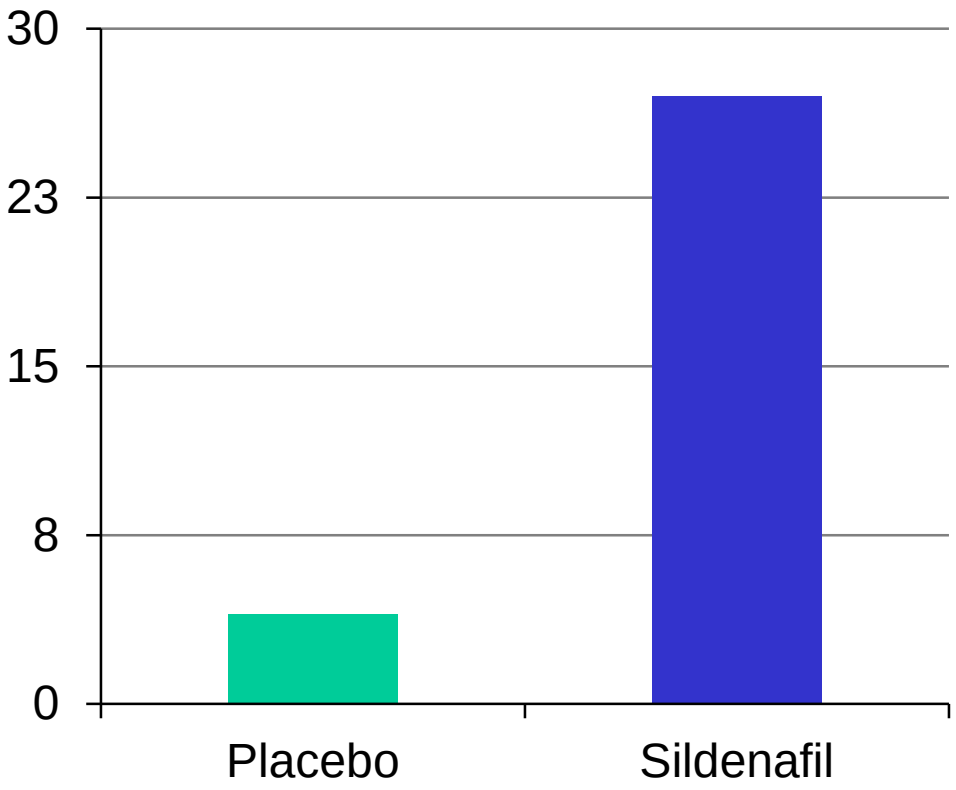
Smooth Muscle Preservation with PDE5-I

- 21 potent men undergoing nerve-sparing radical prostatectomy randomized to 50 or 100 mg sildenafil every other day
- Corpus cavernosum biopsy at surgery & 6 months post op
- The 100 mg group had an increase in mean SM content 6 months after surgery (42.82% vs 56.85%, $p < 0.05$)

Schwartz et al, J Urol. 2004

Sildenafil – Padma-nathan

- 76 men
- Nerve sparing RP
- Sildenafil/placebo daily for 9 mo.
- 2 mo. washout

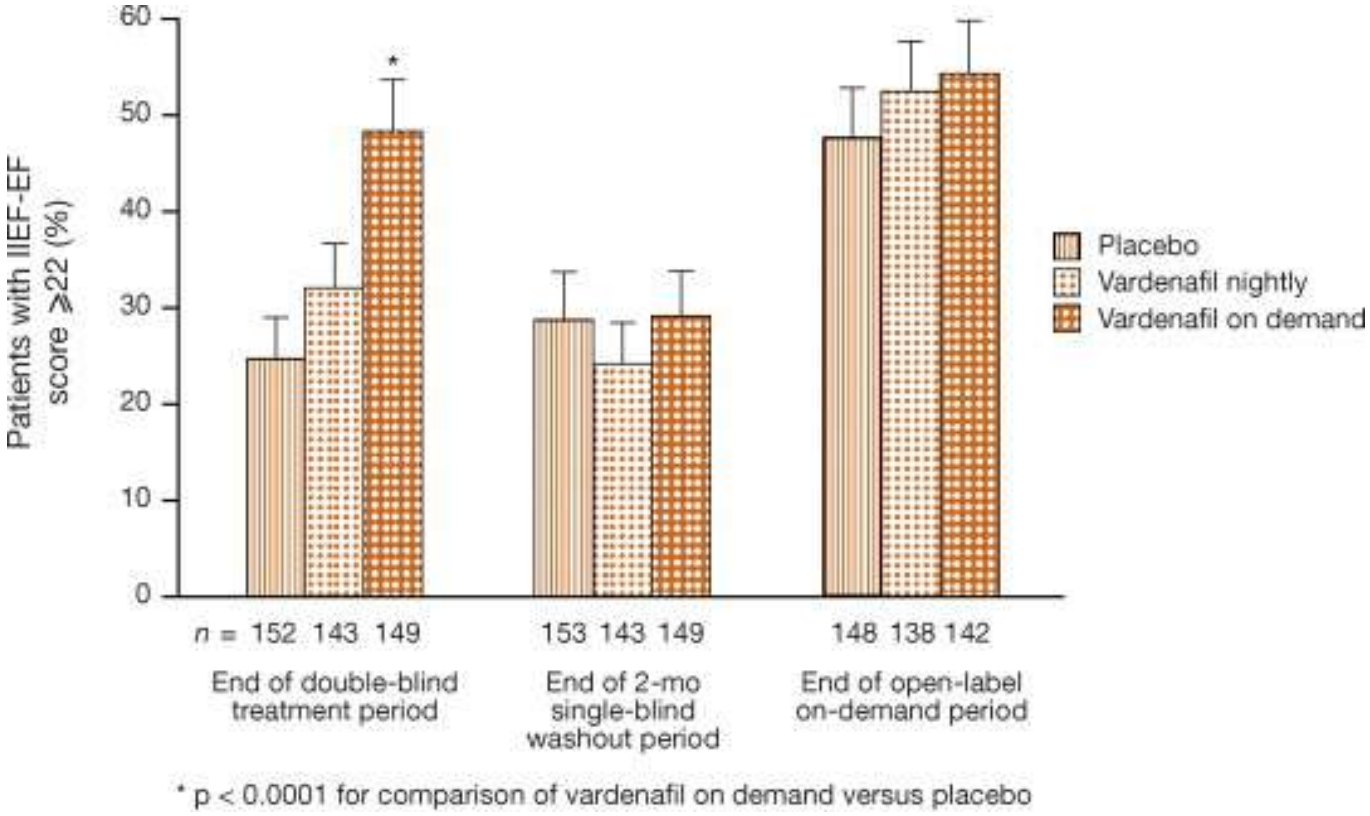


Erections reported as being good enough for satisfactory sexual activity after placebo or nightly sildenafil administration for 36 weeks

Padma-Nathan et al., Int J Impot Res. 2008

Vardenafil – Montorsi 2008

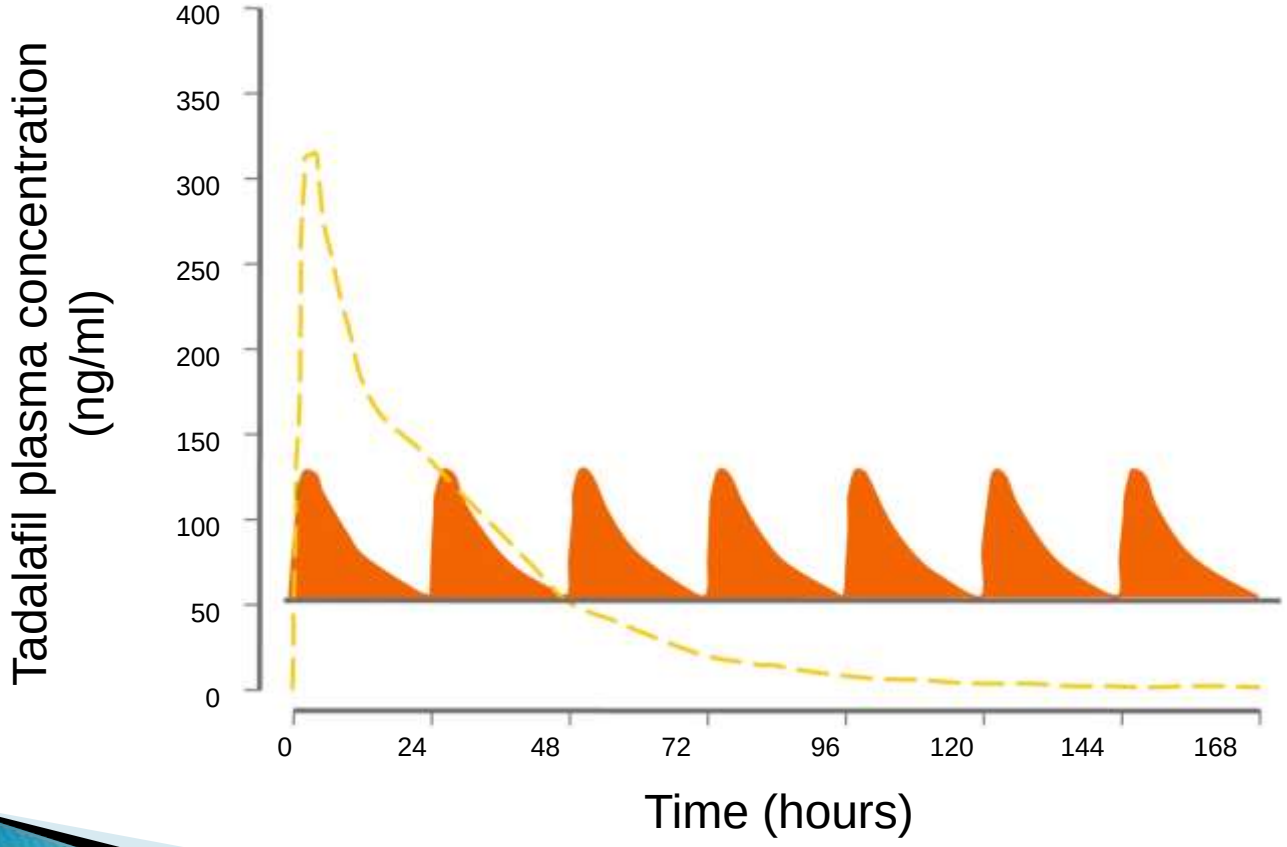
- 435 men
- Nerve sparing RP
- Vardenafil daily
- On-demand
- Placebo
- 2 mo. washout



Montorsi F et al., Eur Urol. 2008

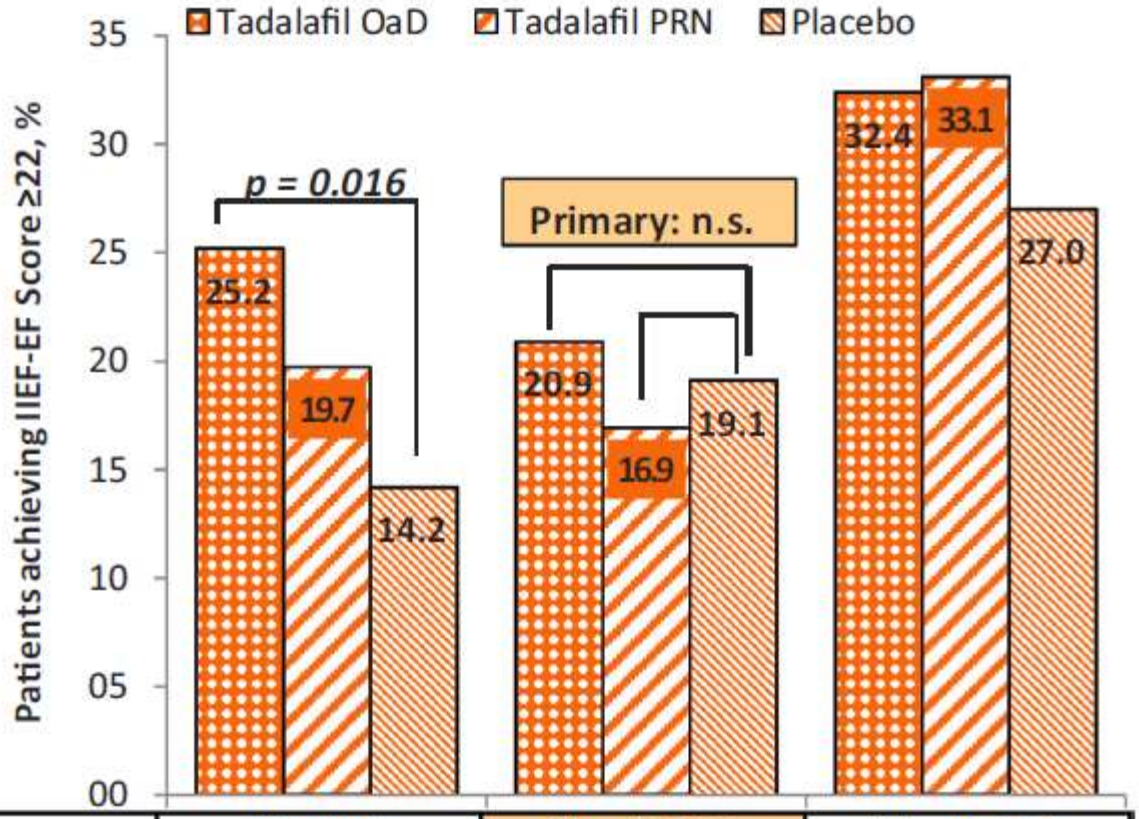
Tadalafil plasma concentration curves

- On-demand and daily dosing over 1 week



Wrishko R et al. J Sex Med 2009

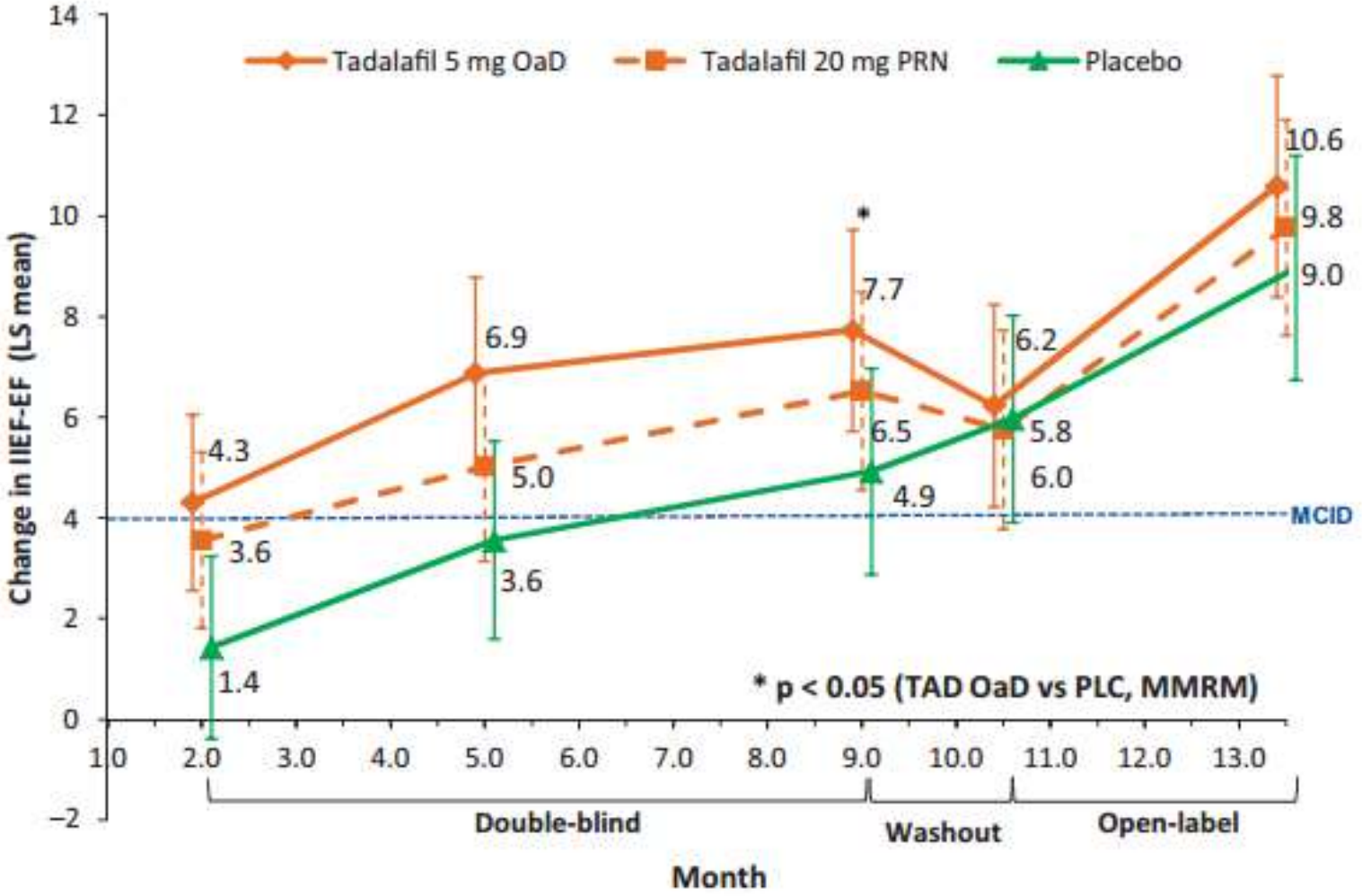
Tadalafil – Montorsi 2014



	Month 9	Month 10.5	Month 13.5
	OR (95% CI); *p value*		
OaD vs Placebo	**2.15 (1.16–3.99); *0.016***	1.14 (0.63–2.06); *0.675*	1.34 (0.79–2.28); *0.273*
PRN vs Placebo	1.50 (0.79–2.85); *0.210*	0.89 (0.48–1.65); *0.704*	1.35 (0.80–2.29); *0.259*

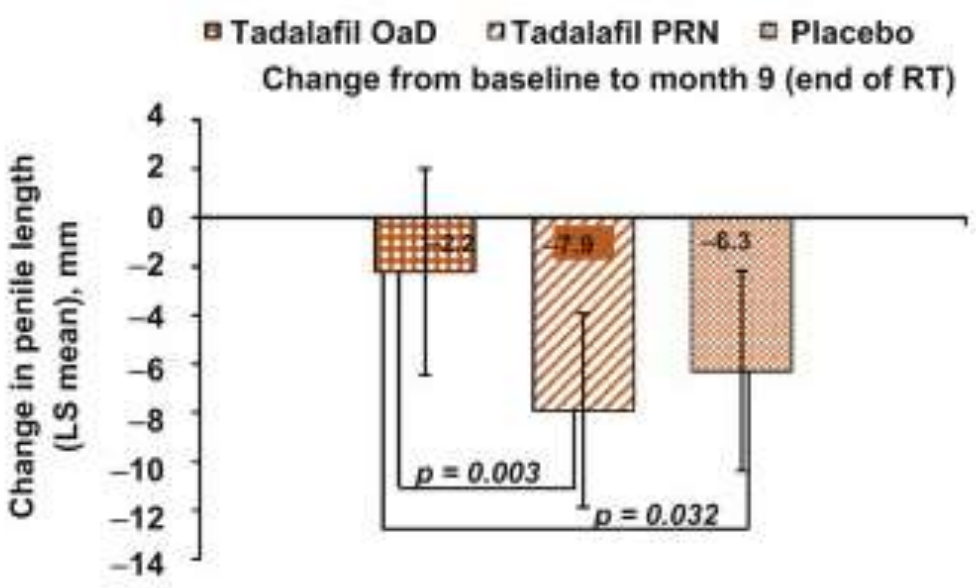
Montorsi F et al., Eur Urol. 2014

Tadalafil – Montorsi 2014



Tadalafil – Montorsi 2014

- Meassurements of penile length as a surrogate meassure of cavernouse tissue integrity



- Daily minus placebo: LS mean: 4.1 mm [95% CI, 0.4–7.8]

Original Article

A prospective, randomized, placebo-controlled trial of on-Demand vs. nightly sildenafil citrate as assessed by Rigiscan and the international index of erectile function

D. J. Kim, D. J. Hawksworth, L. M. Hurwitz, J. Cullen, I. L. Rosner, T. F. Lue, R. C. Dean

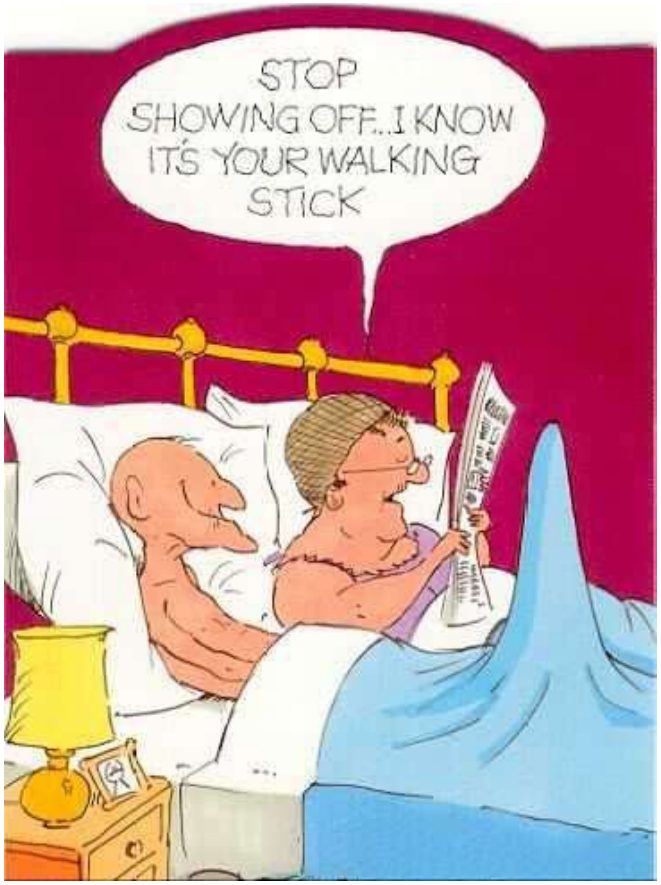
View issue TOC
Volume 4, Issue 1
January 2016
Pages 27–32

Time after surgery	On-demand only (%)	Nightly sildenafil (%)	*p* -value
RigiScan[~, b]			
2 weeks	13.3	22.2	0.41
3 months	20.9	24.4	0.80
6 months	26.8	28.6	1.00
9 months	41.0	45.0	0.82
12 months	26.5	44.4	0.14
13 months[a]	40.0	40.0	1.00

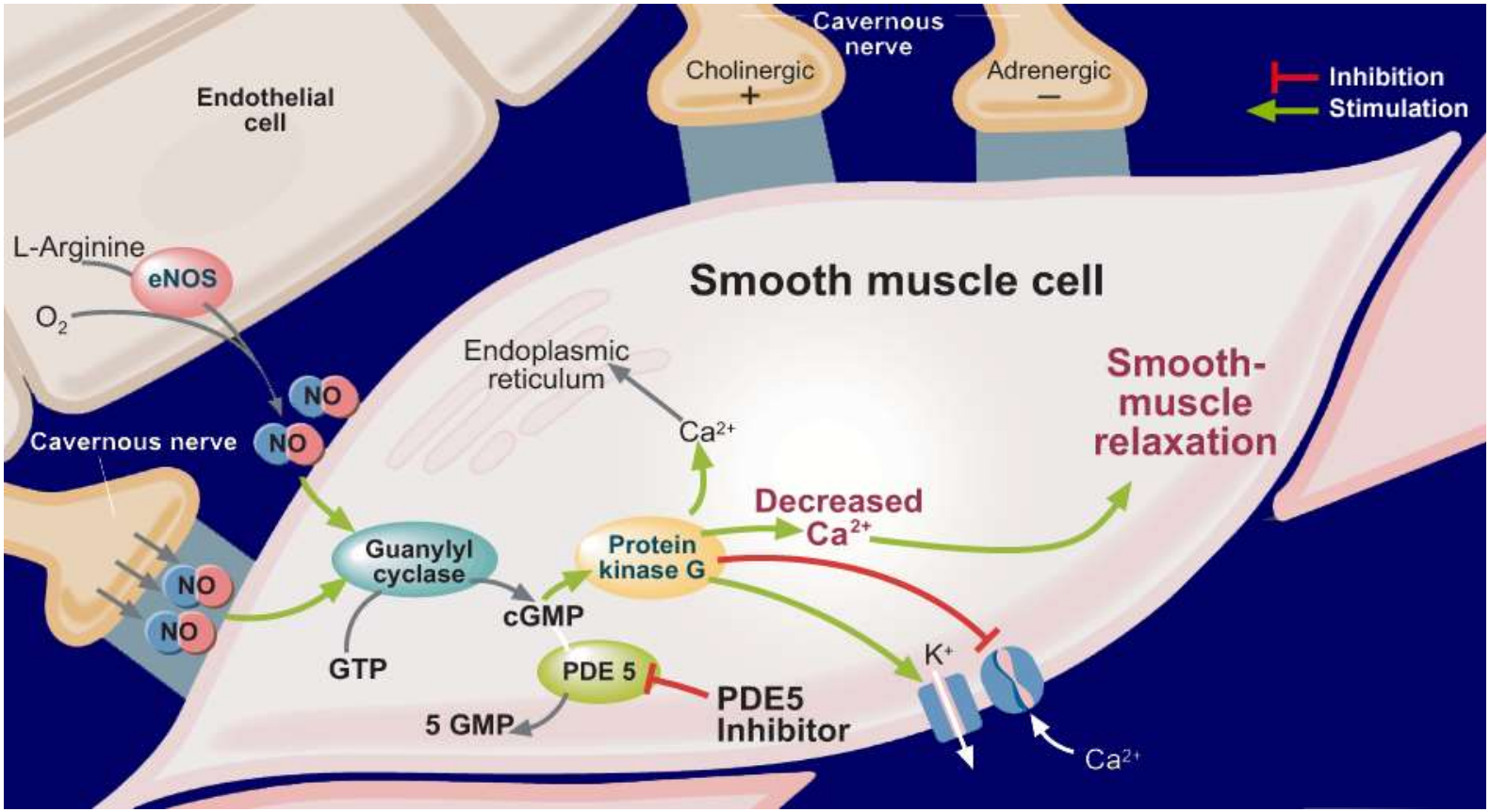
Percent with return to normal erectile function

PDE5-inhibitors conclusion

- PDE5-I is an excellent treatment
  - Daily and on-demand are equal
- PDE5-I offers limited tissue protection
- The treatment has no effect on spontaneous erectile function



Why is the PDE5-I effect so limited?



Other methods

- Injection
- Muse
- Vacuum devices

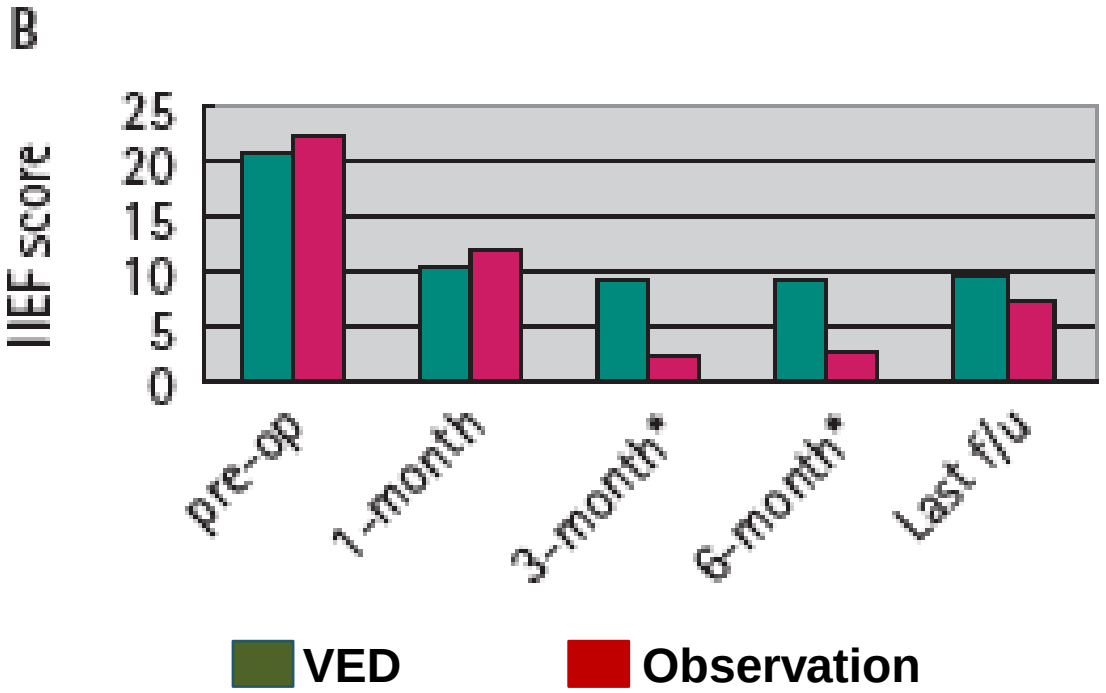
Intracavernosal Injections

- **Alprostadil injections** after nerve-sparing surgery
- 30 patients randomized to injections 3 times per week for 12 weeks or observation
- 12 patients (80%) completed the entire treatment schedule
- **67%** in treatment group and **20%** in control group reported recovery of "spontaneous erections" (**p <0.01**)

Montorsi F et al., J Urol 1997

Vacuum erection device after radical prostatectomy

- 28 Men
- Early or late VED
- Penis rings allowed in treatment group
- VED + PDE5-I for all after 6 months



Köhler et al, BJU int. 2007

Vacuum erection device after radical prostatectomy

- 109 patients randomized to daily VCD or no treatment for 9 months
- Nervesparing and non-nerve-sparing
- Patients unable to perform intercourse with VED excluded
- No statistically significant differences in erectile function between the 2 groups.

Raina et al, BJU Int. 2010

VED and penile shortening

Kohler:

- At 12 month, two out of 17 patients in the early VED group and 5 out of 11 patients in the delayed group had penile shortening of at least 2 cm ($P<0.044$)
- However, there was no actual statistically significant loss in penile length in the delayed treatment group compared to the preoperative measurements

Raina:

- Decrease in penile length reported by: 23% of the successful VED users, 85% of patients who discontinued VED, 63% in the no treatment group
- Penile length assessed by retrospective and subjective patient report

VED

- Post-RP VED therapy may preserve penile length
- VED may function as therapy both early post-prostatectomy and long term
- No effect on spontaneous erectile function

Raina et al, BJU Int. 2010 .
Kohler TS, et al: 2007 BJU Int.

MUSE

- Compared to sildenafil in a randomized study after nerve sparing radical prostatectomy
- 9 months of with intraurethral alprostadil or oral sildenafil citrate (50 mg)
- Return of erectile function was comparable after 1 year of surgery
- No placebo or non-treatment group

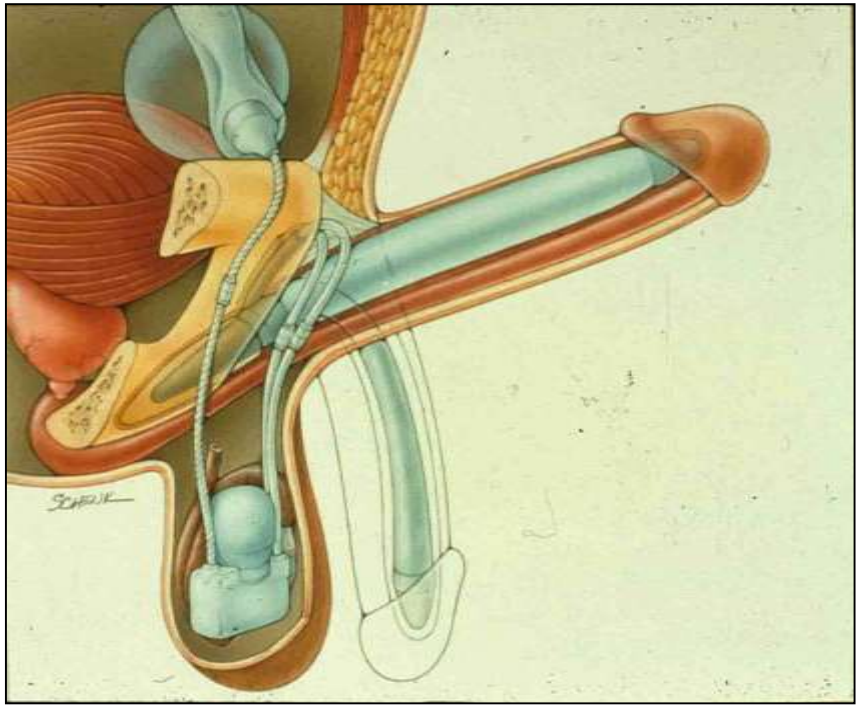
McCullough et al, J Urol ,2010

No other protocols tested in randomized trials!

Treatments do work in motivated patients

- PDE5-inhibitors
  - 85% effective after bilat. NSRP (?)
  - 50% effective after unilat. NSRP
- VED
  - Overall effect ≈ 70%
- MUSE
  - Overall effect ≈ 50%
- Injection therapy
  - Overall effect ≈ 70%

Penile implants provide an effective last option

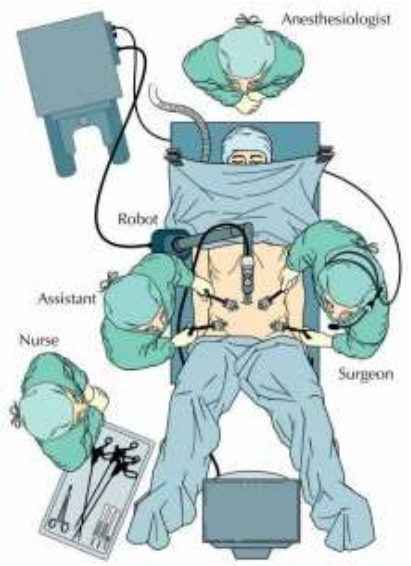


Sexual Rehabilitation

- Encourage sexual activity and intimacy
  - Long periods without sexual activity may cause vaso-occlusive ED
  - Long periods without sexual activity will influence confidence and relationships (men and women)
  - Sex is more than erections and intimacy is key!
- Use erectogenic treatments
  - Theory behind "penile rehabilitation" demands erections
- Focus on the whole person
  - Incontinence
  - Neglected sexual side effects
  - Changes in the patient's life situation (including partner)

Sexual Dysfunction - RP

- Erectile Dysfunction (ED)
  - Most studied
  - Incidence: 6% - 68% *(Ficarra et al. Eur Urol 2012; 62: 418)*
- True Anejaculation (Aspermia) **(anatomo-physiology)**
- Libido Disorders
- **Urinary Incontinence at the Time of Orgasm (Climacturia)**
- **Orgasmic Disturbances**
  - **Altered perception of orgasm**
  - **Anorgasmia**
  - **Orgasm-associated pain (dysorgasmia)**
- **Penile Shortening**
- **"De Novo" Deformity (Curvature – Peyronie's)**



Fode et al. Sex Med Rev 2017, 5: 110

Sexual Dysfunction - RP

MUCH BETTER…

Sexual Dysfunction - RP

- ***Urinary Incontinence at the Time of Orgasm (Climacturia)***
  - ***Incontinence during arousal***
  - **20 – 64%**
  - **Up to 93% at some point following surgery**
  - **Half of the affected patients are bothered with the problem**
  - **Associated with depressed mood, anxiety, worse quality of life**
  - **Tends to decrease throughout the postoperative period**
    - **24% « 12 months / 12% » 12 months** ***(Choi et al. J Urol 2007, 177: 2223)***
  - **No difference between surgical methods**
    - **Better (faster) recovery after robot-assisted RP**

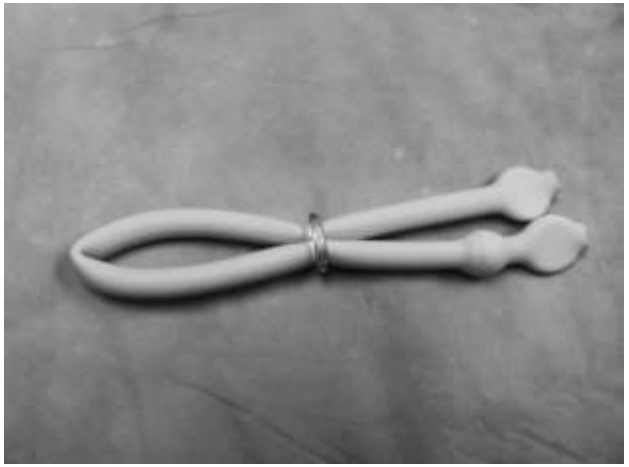
Capogrosso et al. Eur Urol 2016, 70: 223

Frey et al. J Sex Med 2014, 11: 374

Sexual Dysfunction - RP

- ***Urinary Incontinence at the Time of Orgasm (Climacturia)***
  - Removal of internal urethral sphincter
    - together with external urethral relaxation
  - Injury of external urethral sphincter and its supporting structures
    - during surgery
  - Not preserving bladder neck / loss of prostatic urethral length
    - TURP increases risk / loss of penile length is an independent predictor
- ***Management***
  - Emptying the bladder / Condoms / Suitable positions!!!
  - Imipramine 25mg tid
  - Pelvic floor rehabilitation
  - Penile Variable Tension Loop
  - AUS / Slings

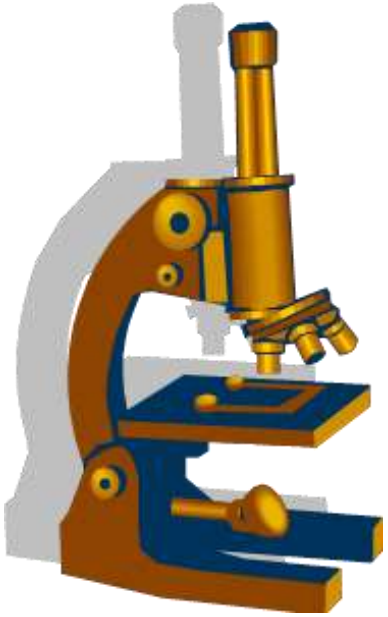
Mehta et al. BJU Int 2013, 111: 500



Frey et al. J Sex Med 2014, 11: 2318
Fode et al. Sex Med Rev 2017, 5: 110

Sexual Dysfunction - RP

- ***Penile Shortening / "De Novo" Curvatures***
  - neural damage /penile hypoxia / smooth muscle apoptosis
  - fibrosis / sympathetic system overactivity
  - *Contradictory data*
  - Protective factors:
    - NS surgery
    - Recovery of erectile function – *return to pre-op?????*
    - Use of PDE5Is
  - High BMI, increased pre-pubic fat – *Buried Penis!!*
  - PD – 16%
    - Risk factor – young age… and white race



- ***Management***
  - "Damage" control – preoperative measurement is paramount
    - Subjective feeling
    - Regular treatment with long-acting PDE5Is / VED?
    - Local hyperthermia therapy (microwaves – 39ºC) – a need for evaluation

Perugia et al. Int J Hyperthermia 2005, 21: 359

Frey et al. J Sex Med 2014, 11: 2318
Fode et al. Sex Med Rev 2017, 5: 110

Sexual Dysfunction - RP

- ***Orgasmic Disturbances*** **- WHY**
  - Anejaculation
  - Local nerve damage
  - Decreased penile stimulation from ED
  - Psychological issues

  - **All patients – "orgasm is somehow different"**
    - Alteration of orgasmic function described in up to 80% of men after RP
    - QoL – marital satisfaction / patient happiness / relationship stability
    - 4% report increased intensity of orgasm *(Barnas et al. BJU Int 2004, 94: 603)*

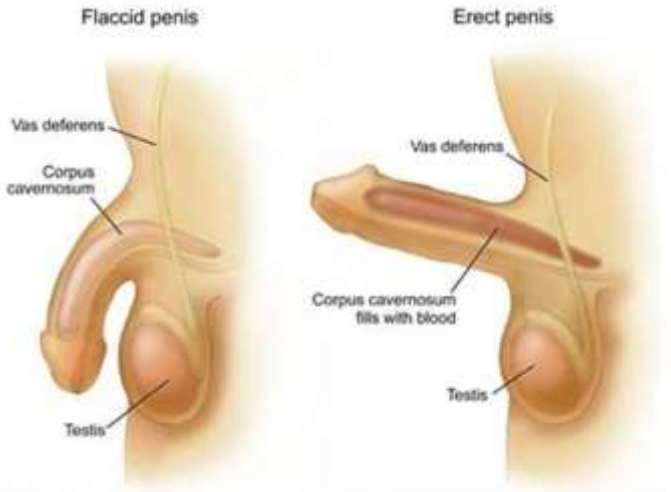
➢ **Altered perception of orgasm**
➢ **Anorgasmia**
➢ **Orgasm-associated pain (dysorgasmia)**

Mah et al. Clin Psychol Rev 2001, 21: 823
Fode et al. Sex Med Rev 2017, 5: 110

Sexual Dysfunction - RP

- ***Altered Perception of Orgasm***
- ***Anorgasmia***

  - "Preserving the ability to achieve an orgasm is considered extremely important in elderly men"
  - Anorgasmia (30 – 40%)
    - Delayed orgasms – 60%
    - Altered perception – 70 to 80%
  - Protective factors:
    - Younger age
    - Nerve-sparing surgery
    - Recovery of erections

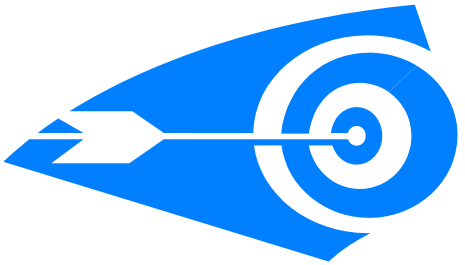


  - Orgasmic function improves with time and orgasmic score increases linearly with erectile function recovery (Salonia et al. J Sex Med 2010, 7: 149)
    - Penile hypossensivity / Hypogonadism
    - Absence of seminal vesicle and prostate contractions ("the feeling")

Fode et al. Sex Med Rev 2017, 5: 110
Clavell-Hernández et al. Sex Med Rev 2018, 6: 124

Sexual Dysfunction - RP

- ***Altered Perception of Orgasm***
- ***Anorgasmia***



  - Orgasmic disturbances
    - Physiologically expected after RP
    - 60% of patients are unware that they would not expel semen after RP

Deveci et al. BJU Int 2016, 118: 641

  - ***Management***
    - ED treatment may improve orgasms
      - PDE5Is – vardenafil *(Nehra et al. J Urol 2005, 173: 2067)*
        - probably due to improvement in erectile function
    - Cabergoline!!!
    - Psychological aspects
      - Partner involvement
      - Communication training / Cognitive-behavioral therapy
      - Orgasm even with persistent ED

Molton et al. J Psychosom Res 2008, 64: 527

Sexual Dysfunction - RP

Orgasm-Associated Pain (Dysorgasmia)

- Incidence: 3 to 20% after RP
- Moderate in severity / Less than 1m in most cases
- Most commonly experienced in the penis, testis and rectum
- Intensity and frequency decrease with time
- Protective factors:
  - Older age
  - Robot-Assisted Laparoscopic RP (lower incidence, BUT same recovery time…)
- Increased risk:
  - Sparing seminal vesicle tips (filling and contraction ⇒ PAIN)

Clavell-Hernández et al. Sex Med Rev 2018, 6: 124

  - Vesicourethral anastomosis spasms / PF muscle dystonia
  - ROBOT – lack of disturbance to levator ani muscles

Koeman et al. Br J Urol 1996, 77: 861
Capogrosso et al. Eur Urol 2016, 70: 223

Sexual Dysfunction - RP

Orgasm-Associated Pain (dysorgasmia)

Management

- Encourage patients to stay sexually active
  - TIME is friendly!!!
- Alpha-blockers (tamsulosin) – by acting on SV contraction
- Psychosexual therapy
- Nonsteroidal anti-inflammatory drugs

"It is important for clinicians to inform patients that, regardless of the lack of ejaculate and sometimes erection, they should still pursue sexual activity and be able to achieve orgasm after RP"

Clavell-Hernández et al. Sex Med Rev 2018, 6: 124

Barnas et al. Eur Urol 2005, 47: 361
Fode et al. Sex Med Rev 2017, 5: 110

… and remember the partner!

ED/RP – General Guidelines

- **GENERAL ED GUIDELINES (EAU 2017)**

Recommendations	LE	GR
Offer men on androgen deprivation therapy, twelve weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	1a	A
Offer men with T1-T3 disease specialist nurse led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	1b	A

Recommendations	LE	GR
Enact lifestyle changes and risk factor modification prior to or accompanying erectile dysfunction (ED) treatment.	1a	A
Start pro-erectile treatments at the earliest opportunity after radical prostatectomy.	1b	A
Treat a curable cause of ED first, when found.	1b	B
Use phosphodiesterase type 5 inhibitors (PDE5Is) as first-line therapy.	1a	A
Assess all patients for inadequate/incorrect prescriptions and poor patient education, since they are the main causes of a lack of response to PDE5Is.	3	B
Use vacuum erection devices as a first-line therapy in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED.	4	C
Use intracavernous injections as second-line therapy.	1b	B
Use implantation of a penile prosthesis as third-line therapy.	4	C