

# Penile Rehabilitation After Radical Prostatectomy

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The widespread use of PSA testing has led to an increasing number of men being diagnosed with early stage prostate cancer, and at younger ages. Radical prostatectomy (RP) is a definitive treatment option for these patients, with excellent long-term results. Despite the advances made with nerve-sparing surgical techniques and the use of robotic-assisted laparoscopic procedures, the incidence of post-prostatectomy erectile dysfunction (ED) remains significant. Return of erectile function is not immediate, and may occur over 6 months to 4 years. In the Prostate Cancer Outcomes Study approximately 60% of men were impotent 18 months after RP; at 5 year follow-up, only 28% of men reported erections firm enough for intercourse, either with or without an erectile aid.<sup>1,2</sup> Literature published over the last decade shows widely disparate rates of erectile function and dysfunction following RP. The incidence of complete ED, partial erectile function, and intact erectile function after RP ranges from 26-100%, 16-48%, and 9-86%, respectively.<sup>3</sup> It is important to understand that after radical prostatectomy the ability to achieve the sensation of orgasm is not affected. However, ejaculation of seminal fluid no longer occurs since the seminal vesicles and prostate are absent. Patients will generally experience a "dry" orgasm although some patients may leak a small amount of urine with orgasm or secrete a drop of clear pre-ejaculate fluid from the glands of Litre in the urethra.

With a decreasing average age at prostate cancer diagnosis and an increasing number of radical prostatectomies performed annually, postoperative sexual function is an important concern for many patients. In a prospective cohort of 580 patients treated with RP, external beam radiation therapy or brachytherapy for localized prostate cancer, sexual bother was much more common than urinary or bowel bother at all time points, regardless of the primary therapy.<sup>4</sup> Some patients value sexual function so highly that they choose prostate cancer therapy that offers better potency with lower life expectancy than vice versa.<sup>5</sup>

Patient age, preoperative potency status, and extent of neurovascular bundle preservation have been identified as factors predictive of potency recovery after RP.<sup>6</sup> Penile rehabilitation after radical prostatectomy has been advocated as a means of preserving erectile function following surgery. We review the pathophysiology of post-prostatectomy ED, the rationale for early penile rehabilitation, and the current strategies.

## PATHOPHYSIOLOGY OF POST-PROSTATECTOMY ED

The normal erectile process involves relaxation of the smooth muscles in the corpora cavernosa of the penis, leading to increased blood flow into the penis. As a result of the engorgement of the corporal tissue, venous drainage out of the corpora is compressed against the tunical coating of the corpora, leading to decreased venous outflow (veno-occlusion).<sup>7</sup> At the molecular level, cavernosal smooth muscle relaxation is dependent on nitric oxide (NO) from cholinergic nerve endings or sinusoidal endothelium, which then activates cGMP pathway. Phosphodiesterases (PDE) interfere with this process by hydrolyzing cGMP.

Radical prostatectomy leads to an extended period of intracorporal hypoxia, due to decreased arterial flow and chronic absence of erections. Penile hypoxia impairs NO synthesis and promotes collagen synthesis and cavernosal fibrosis. Progressive cavernosal fibrosis leads to veno-occlusive dysfunction and increased venous leak in affected patients. These changes result in permanent ED and may also cause the penis to shorten due to scar tissue.

Etiologies of ED following RP include nerve injury, arterial trauma, and veno-occlusive dysfunction.<sup>8,9</sup> Some degree of neuropraxia occurs even in bilateral nerve-sparing RP, despite meticulous surgical dissection. The recovery of nerve function occurs slowly over 6 months to 4 years, as neuropraxia resolves.<sup>10</sup> Arteriogenic ED occurs due to the transection of accessory pudendal arteries, which can be difficult to visualize or preserve at the time of RP. Decreased

arterial inflow leads to penile hypoxia and contributes to penile fibrosis and disuse-related corporal smooth muscle atrophy. Venous leak, or corporal veno-occlusive dysfunction, is the most common form of ED after following RP.<sup>3</sup>

## RATIONALE BEHIND PENILE REHABILITATION

Penile rehabilitation is a program to improve penile healing in an attempt to increase the chance of return of erectile function after prostate cancer therapy, by increasing cavernosal tissue oxygenation, and decreasing tissue fibrosis and apoptosis. In 1997, Montorsi postulated that early postoperative use of alprostadil injections into the penis to induce erections would lead to increased corporal oxygenation and avoid structural changes in corporal tissue related to prolonged absence of postoperative erections.<sup>11</sup> In this small randomized study of three times weekly intracavernosal alprostadil (PGE1) vs. no treatment, potency in the treatment group was 67% vs 20% without treatment. During erection, oxygen tension in the corpus cavernosum changes from 30-40 mmHg in the flaccid state to 70-100 mmHg in the erect state.<sup>3</sup> Cavernosal oxygenation is therefore considered important for erectile tissue health. The early use of hyperbaric oxygen therapy in rats after cavernosal nerve injury showed an increase in the intracavernosal pressure-to-mean arterial pressure ratio from 30% on room air to 55% on hyperbaric oxygen.<sup>12</sup>

Animal studies demonstrate a protective effect of phosphodiesterase inhibitor (PDE5-i) therapy on cavernosal smooth muscle mass.<sup>13</sup> Rats subjected to bilateral cavernosal nerve resection develop corporal fibrosis and veno-occlusive dysfunction. When treated with PDE5-inhibitors, researchers noted an increase in smooth muscle content vs. collagen, normalization of veno-occlusive dysfunction, and a decrease in the smooth muscle apoptotic index.<sup>14-17</sup> In animals, both functional and structural consequences of cavernous nerve injury can be ameliorated by PDE5-i therapy.

The data in humans have been mixed. A randomized controlled study of nightly sildenafil vs. placebo in 76 men after nerve-sparing RP demonstrated markedly increased return of spontaneous erectile function after 36 weeks in the sildenafil group (27% vs. 4%).<sup>18</sup> Unfortunately, researchers did not study the outcomes beyond one year and the potency rate in the placebo arm was lower than historical controls. The use of PDE5-i therapy has also been associated with improved histological outcomes. In men receiving sildenafil every other night after RP, no significant differences were noted in collagen or smooth muscle content 2 and 6 months after RP compared to preoperative biopsies, indicating prevention of cavernosal fibrosis.<sup>19,20</sup> While the primary goal of penile rehabilitation is to promote the return of spontaneous erectile function, a secondary goal is to improve the ability of patients to become responders to erectogenic medications. In a study comparing outcomes in men who underwent penile rehabilitation with either sildenafil or intracavernosal injection therapy (ICI) vs. those who did not, preservation of erectile function was noted in 52% of the rehabilitation group vs. 19% in the non-rehabilitation group 18 months postoperatively.<sup>21</sup> Furthermore, penile rehabilitation improved patient response to sildenafil (64% vs. 24%) and ICI (95% vs. 76%), and resulted in a significantly earlier response to sildenafil compared to no rehabilitation.<sup>21</sup> Together, results from the above studies provide evidence to support early institution of penile rehabilitation after RP.

### **THERAPEUTIC OPTIONS FOR PENILE REHABILITATION**

Early treatment options for erectile dysfunction after RP include oral PDE5 inhibitors, intraurethral medications and intracavernosal injections (PGE1, papavarine, and phentolamine combinations), and vacuum erection devices (VED) without the constriction ring.

Interest in the use of VEDs in penile rehabilitation protocols stems from its high patient compliance rate and its affordability, due to insurance approval. A randomized study of the daily use of VED vs. no treatment after RP demonstrated significantly improved erections

for both nerve-sparing and non-nerve-sparing RP patients who used VED compared to controls.<sup>22</sup> Even a single use of VED after RP increased corporal and glanular oximetry relative to baseline.

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## **Some patients ... choose prostate cancer therapy that offers better potency with lower life expectancy than vice versa**

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RP has a significant impact on penile length and girth, with some decrease in penile stretch length reported in up to 71% of patients, and a mean reduction in penile volume of 22%.<sup>23-25</sup> Nerve-sparing surgery and recovery of erectile function have been shown to have an independent protective effect on penile length loss.<sup>26,27</sup> The early use of a VED has been shown to reduce the likelihood of significant penile shortening from 48% in historical controls to 3%.<sup>28</sup>

Alprostadil may be more effective than oral PDE5-i for the early treatment of erectile dysfunction after RP because it does not require nerve function.<sup>29</sup> A controlled study of the early use of intraurethral alprostadil three times weekly after RP demonstrated significantly improved IIEF-5 scores, more frequent sexual activity, and greater return of natural erections sufficient for vaginal intercourse at 9 months postoperatively in patients who used alprostadil vs. patients who did not use any treatment.<sup>30</sup> Recent data also suggest that low dose nightly alprostadil significantly increased flaccid penile oxygen saturation when compared to sildenafil.<sup>31</sup> Disadvantages of alprostadil therapy include urethral irritation, cost, and lack of insurance coverage.

The use of oral PDE5-i for penile rehabilitation has been associated with preserved corporal smooth muscle mass and decreased fibrosis, as described above. A recent meta-analysis clearly demonstrates improvement in erectile function in two-thirds of participants and successful intercourse in 28-50% of participants.<sup>32</sup> The optimal dose and frequency of dosage of

PDE5-i therapy has not been established. On the contrary, two recent studies evaluated the efficacy of a nightly or every-other-day PDE5-i regimen compared to a regimen of using the medication only when attempting sexual activity (on-demand dosing). No difference was demonstrated between the two regimens.<sup>33-36</sup>

ICI, although highly effective at inducing erection, has the obvious side effects of being invasive and potentially painful. While studies have shown that combination therapy using ICI and oral PDE-5i facilitates early sexual intercourse and earlier return of spontaneous function, and high success rates even in the setting of other medical comorbidities, patient compliance is low.<sup>7,37</sup>

### **THE BROWN UNIVERSITY EXPERIENCE**

Most penile rehabilitation programs combine erectogenic therapies to optimize patient compliance as well as cost and therapeutic outcome. At the Men's Health Center at Miriam Hospital patients are seen for an initial consultation 4-6 weeks after radical prostatectomy. Our rehabilitation regimen consists of daily use of a VED for 10 minutes, without a constriction ring, and three times weekly intraurethral administration of compounded Trimix gel (alprostadil, phentolamine and papaverine) for the first postoperative year. Patients are encouraged to try oral PDE5-i on a monthly basis to assess for return of any erectile function. Sexual activity is encouraged, whenever desired by the patient and his partner, and PDE5-i or intracavernosal injection therapy is prescribed when required as an erectogenic aid to allow for sexual activity during the rehabilitation program.

### **FUTURE DIRECTIONS**

More studies are needed to determine optimal dosing, type, and frequency of medications for the rehabilitation programs. Whether on-demand medication to induce erections for sexual activity are as effective as nightly or several night per week medication in return of erectile function remains controversial. Recent studies have suggested a potential role for erythropoietin in erectile preservation due to its role as a neurotrophic agent and a stimulator of erythropoiesis under hypoxic conditions.<sup>38</sup>

## CONCLUSION

Despite the limitations of the clinical studies, including short follow-up, small number of patients, retrospective nature, or lack of consistent controls, the popularity of penile rehabilitation after RP is growing. No perfect regimen yet exists, and the choice of regimen will need to account for cost, effectiveness and patient compliance.

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## Disclosure of Financial Interests

The authors have no financial interests to disclose.

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