

# Current rehabilitation strategy: clinical evidence for erection recovery after radical prostatectomy

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**Abstract:** Erectile function (EF) recovery remains a prominent functional outcome underachievement of radical prostatectomy (RP), despite the success of anatomic “nerve-sparing” technique and its recent refinements in the modern surgical era. Delayed (for as much as a few years) or incomplete (partial and unusable) EF recovery commonly occurs in many men still today undergoing this surgery. “Penile rehabilitation”, alternatively termed “EF rehabilitation”, originated formally as a therapeutic practice approximately 15 years ago for addressing post-RP erectile dysfunction (ED) beyond conventional ED management. Although the premise of this therapy is conceptually sound and generally accepted, in reference to the implementation of strategies for promoting EF recovery to a naturally functional level in the absence of erectile aids (distinct from the premise of conventional ED management), the optimal manner and efficacy of currently suggested therapeutic strategies are far less established. Such strategies include regimens of standard ED-specific therapies (e.g., oral, intracavernosal, and intraurethral pharmacotherapies; vacuum erection device therapy) and courses of innovative interventions (e.g., statins, erythropoietin, angiotensin receptor blockers). An endeavor in evolution, erection rehabilitation may ideally comprise an integrative program of sexual health management incorporating counseling, coaching, guidance toward general health optimization and application of demonstrably effective “rehabilitative” interventions. Ongoing intensive discovery and rigorous investigation are required to establish efficacy of therapeutic prospects that fulfill the intent of post-RP erection rehabilitation.

**Key Words:** Erectile dysfunction; penile erection; pharmacotherapy



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## Introduction

Erectile dysfunction (ED) remains a significant clinical complication risk following major genitourinary pelvic surgeries such as radical prostatectomy (RP). Today, functionally intact men undergoing RP uniformly may expect rapid return to occupational and recreational life activities (within a few weeks to months), early recovery of urinary control (within a few months), and negligible changes in bowel function, although aspects of sexual function recovery are predictably less favorable: they are either forever changed or they may require significant time

durations to improve or recover (months to years).

These recovery expectations actually represent substantial progress in the field, and functional outcomes in the past were far less encouraging. The advance of anatomic “nerve-sparing” RP, now commonplace in the past 30 years, has contributed significantly to functional preservation overall and more specifically to erectile function (EF) recovery, which was all but non-existent prior to its use (1,2). The recent addition of laparoscopic and robotic procedures to the surgical armamentarium as “minimally invasive” surgical options has not unequivocally improved EF recovery outcomes relative to open surgery results, and

practitioners of RP by any surgical approach today continue to observe delayed and incomplete EF recovery in their patients (3,4).

Accordingly, an ongoing major focus in the modern utilization of RP surgery is the optimization of EF outcomes postoperatively. The concept of “penile rehabilitation” or “EF rehabilitation” has been coined and championed much as a quasi-practice standard in the field to promote EF recovery, although evidence of success of this practice is ambiguous if not lacking (5,6). The objective of this essay is to evaluate the role of rehabilitative strategies in preserving EF following RP. It begins with a critical examination of such strategies that have been frequently touted or shown early promise as potentially efficacious options at clinical investigative levels. This exercise lends insights for prescribing a practical management scheme for post-RP ED management that incorporates erection rehabilitative strategies. The essay concludes with a perspective on possibilities ahead for advancing this field.

### **Erectile dysfunction after radical prostatectomy**

Any discussion of EF recovery outcomes following RP must always begin with an assessment of the problem: the extent and manner by which EF is impaired by the surgery. Historically, it was understood that complete loss of erections was the norm following RP resulting from unavoidable injury of vital peri-prostatic pelvic structures that are associated with erection physiology, erection-stimulating cavernous nerves and penile blood-filling vasculature. Steady research work in the field has led to improved knowledge of the anatomical and functional requirements for penile erection and rigor in defining the surgical alteration of this functional outcome. Current perspectives on this subject suggest a likely scope of EF recovery rates in the order of 40-80% for the 65 year-old or younger man who is functionally intact prior to the surgery and undergoes a maximal nerve-sparing surgical procedure with sufficient time of as much as 18 or more months to assess maximal recovery (7). It is acknowledged that accurate statistics bearing on complete or partial EF recovery remain elusive given existing variations in the quality of execution of anatomical RP and also in the assessment of EF outcomes afterwards (8,9).

Amidst the ongoing debate about the exact extent of EF recovery after RP currently in the field, it is widely accepted that this outcome is commonly delayed and incompletely restored prompting many men to seek interventions,

i.e., EF aids or ED therapies, in the interim of expected functional recuperation and for extended intervals after RP as well (10). Several strategies have been proposed to address this shortcoming, although they have been geared primarily toward 2 main tactical approaches: intraoperative interventions and postoperative interventions.

### **Strategic concepts for improving erectile function recovery**

Intraoperative interventions have been sought to extend concepts of anatomic RP surgery applying novel ways that protect or promote the function of nerves, vasculature and erectile tissue itself required for penile erection. Specific strategies have included refinements in surgical technique (e.g., visual magnification, high anterior release of the levator fascia, intrafascial neurovascular bundle preservation) (11,12), procedures for neurovascular bundle localization and preservation (e.g., electrostimulation, mapping technologies) (13-15), cavernous nerve reconstitution (e.g., nerve grafting) (16,17), and cavernous nerve and erectile tissue health protection (e.g., growth factors, corticosteroids, erythropoietin) (18,19). Similarly, intraoperative preservation of accessory pudendal vasculature supplying the penis has been proposed (20). Although all of these approaches are rational and possibly offer benefit, for many their roles have been suggested based on preliminary, uncontrolled investigations such that their therapeutic impacts remain unclear. Some strategies are also implausible based on their onerous administrations and limited indications amid current surgical-oncologic scenarios.

Postoperative strategies have amply suited the aims of erection rehabilitation. Broadly viewed, this practice encompasses the institution of any form of ED treatment that momentarily or permanently overcomes erection loss resulting from an EF insult (e.g., RP), irrespective of EF preservation or recovery considerations. However, an alternative, more exclusive premise is associated with erection rehabilitation: the implementation of an early post-EF insult (e.g., post-operative) program of intervention *with the intention of facilitating the return of natural EF and resumption of medically unassisted sexual activity.*

Proponents of the latter perception identify a role for penile rejuvenative interventions, which theoretically aim to maintain EF by activating normal physiologic processes of penile erection (21,22). These interventions typically exploit sexual stimulatory or blood flow conditions in the penis, which theoretically exert: (I) preserved cavernosal

oxygenation, (II) protected endothelial function, and (III) reduced erectile tissue damage resulting from cavernous nerve injury. Therapy conceptually consists of a finite course of administration according to a specific protocol. Pharmacological interventions, among standard ED treatments, have been most frequently borrowed for this purpose, owing to their clinical availability, tolerability and general safety. These options include oral treatments, intracavernosal injections, and intraurethral suppositories. Other conventional ED interventions such as vacuum erection devices (VED) have also been proposed. Besides these “ED-specific” treatments, several conceptually “outside-the-box” therapeutic prospects targeting dysfunctional erection physiologic components have also been recently developed and explored.

### Vasoactive pharmacotherapy

The landmark report credited with originating the concept of post-RP erection rehabilitation was published approximately 15 years ago (23). The study applied intracavernosal pharmacotherapy according to the rationale that programmed vasoactive medications delivered into the cavernous tissue would limit hypoxia-induced tissue damage. The protocol involved injections of alprostadil 3 times weekly for 12 weeks after nerve-sparing RP, showing that recovery of spontaneous erections at 6 months following surgery occurred in 8 of 12 (67%) patients receiving this therapy compared with 3 of 15 (20%) patients managed by observation alone ( $P < 0.01$ ). The investigation suggested a potential benefit to this rehabilitative strategy. However, concerns of this study include low patient enrollment, lack of long-term assessment, and lack of treatment blindness, which may have biased results towards treatment success. Other such studies of intracavernosal pharmacotherapy for erection rehabilitation have also suggested potential benefit (24), although their similarly uncontrolled, non-randomized study designs limit conclusive statements about efficacy of this treatment. Besides the onerousness of this intervention, the lack of controlled clinical trial evidence significantly hampers the weight of support for intracavernous pharmacotherapy for the purpose of penile rehabilitation.

With the advent of effective on-demand oral pharmacotherapy for ED in the form of phosphodiesterase type 5 (PDE5) inhibitors approximately 15 years ago, the notion to bring forward this therapy as erection rehabilitation in the post-RP setting was predictable. The rationale for another vasoactive therapeutic approach

targeting the cavernous tissue seemed reasonable, and its administration in a much more tolerable fashion than by traumatic penile injections also seemed advantageous. A host of preclinical studies in rodent animal models of cavernous nerve injury mimicking the conditions of RP have been done suggesting rehabilitative efficacy of PDE5 inhibitors (25-28). Non-randomized clinical studies have suggested benefit using this approach (29,30). However, limited controlled investigations in an erection rehabilitative context have been done, in contrast with the plethora of controlled clinical trials designed to evaluate PDE5 inhibitors for ED treatment indications.

The well-known double-blind, randomized, placebo-controlled clinical trial involving the use of sildenafil citrate by postoperative nightly administration beginning 4 weeks after nerve sparing RP for 36 weeks showed that by 1 year postoperatively EF recovery as assessed by standardized International Index of Erectile Function (IIEF) questionnaire and objective Rigiscan monitoring occurred in 14 of 51 (27%) patients on therapy compared with 1 of 25 (4%) patients on placebo ( $P < 0.05$ ) (31). The REINVENT (Recovery of Erections: Intervention with Vardenafil Early Nightly Therapy) study, which was a randomized, double-blind, double-dummy, placebo-controlled evaluation of nightly *vs.* on demand vardenafil hydrochloride for 9 months, starting within 1 month after nerve-sparing RP, showed that by 1 year postoperatively EF recovery as assessed by normative IIEF- EF Domain score and Sexual Encounter Profile question 3 (successful intercourse success rate) was equivalent after washout and open-label periods in vardenafil-treated and placebo-treated groups (32). Notwithstanding methodologic and interpretative concerns that have been raised in association with these studies that have limited firm conclusions, the conflicting support for the role of PDE5 inhibitors for erection rehabilitation after RP leaves unanswered the question as to whether this therapy is effective for this purpose.

Intraurethral pharmacotherapy has offered an alternative locally administered vasoactive therapy for erection rehabilitation, conceivably representing a more tolerable approach than intracavernous injections. In a representative investigation that enrolled 56 men in a protocol using intraurethral alprostadil 3 times weekly for 6 months after nerve-sparing RP, 15 (29%) patients reported having natural erections sufficient for satisfactory intercourse at 6 months whereas 18 men withdrew (33). This study seemingly suggests benefit of this therapy particularly in highly motivated individuals, although any conclusion of

therapeutic effectiveness is limited by patient selection bias, lack of long-term assessment, and lack of treatment blindness. The study also revealed the procedural challenges of intensive, self-administered, semi-invasive therapies for erection rehabilitation. A more recent randomized trial comparing intraurethral pharmacotherapy and oral pharmacotherapy consisting of sildenafil after nerve sparing RP showed a trend toward earlier return of EF for both forms of treatment based on IIEF-EF Domain scores, although the benefit was slightly greater for the former (34). Similar shortcomings observed in this trial were substantial attrition rates (30% for intraurethral pharmacotherapy, 19% for oral pharmacotherapy) as well as lack of a control group.

### **Mechanical therapy**

VED therapy provides an altogether different ED-specific therapeutic approach for erection rehabilitation, by mechanically inducing “negative-pressure” as a means to draw blood into the penis. Several protocols using VED daily post-RP have been reported under the contention that this treatment favorably preserves EF. In one study, 35 of 36 compliant patients did not show penile shrinkage (>1 cm) at 3 months after RP (35). In another study, IIEF scores were significantly higher and stretched penile length was preserved in the intervention group compared with the control group at 3 and 6 months after RP (36). In a further study, utilizing a prospective randomized study design in 109 men, 17% of patients treated with VED *vs.* 29% of controls reported spontaneous erections sufficient for sexual intercourse at 9 months after nerve-sparing RP and there was a substantial dropout rate (18% at 3 months into treatment) (37). These studies broadly suggest the possible erection rehabilitative benefit of VED therapy. However, the firmness of such a conclusion is restrained based on study limitations including imperfect control groups, small patient populations, relatively short-term follow-up assessments, lack of an intention-to-treat analysis, and indirect evidence of EF recovery benefit.

### **“Innovative” therapies**

Statin therapy has been proposed as an EF preservative strategy following RP, based on the premise that it may exert improved oxygenation for cavernosal tissues, vascular endothelial protection, or possibly neuronal regenerative or protective effects. In a trial of 50 preoperatively potent men

without hypercholesterolemia who were randomized either to a treatment group receiving oral atorvastatin daily in combination with sildenafil as needed or to a control group receiving only sildenafil as needed for 90 days after nerve-sparing RP, the treatment group demonstrated more than a 2-fold greater improvement in functional IIEF-5 scores and intercourse satisfaction scores by 6 months postoperatively (55% *vs.* 26.1%,  $P=0.068$ ) (38). This study, performed using rigorous clinical trial methodology, suggests a convenient, well-tolerated strategy for improving EF recovery post-RP.

Erythropoietin has also been investigated as a possible EF preservative or restorative strategy following RP. The rationale for using this cytokine-hormone is based on basic scientific evidence of its less familiar beneficial effects as an anti-apoptotic agent and tissue growth factor (39,40). Preclinical findings in rodent animal models of cavernous nerve injury mimicking RP conditions have suggested its potential clinical efficacy (41). Further preclinical work has confirmed its receptor localizations in human cavernous nerves and cavernous tissue (42). At a clinical level, a retrospective analysis of a single high-dose erythropoietin injection on the day prior to nerve-sparing RP found that 7 of 15 (47%) treated patients *vs.* 3 of 19 (16%) untreated patients achieved functional erections at designated IIEF-5 functional levels at 12 months postoperatively ( $P<0.05$ ) (43). The therapy was well tolerated and exerted no clinically significant adverse events such as vascular thrombosis or hypertension. This study suggests that erythropoietin may confer erection rehabilitative benefit and be safe clinically at least with short-term preoperative use. However, the obvious shortcoming of this study is its retrospective, unblinded design that presents potential recall and selection biases. The promotion of this therapy must await further investigation by prospective, randomized, controlled trial design.

Angiotensin type 2-receptor blocker (ARB) therapy has been explored as having potential beneficial effects for post-RP erection rehabilitation as well, encouraged by preclinical work in rodent animal models of RP suggesting the potential role of this therapy in this setting (44). In a retrospective analysis of its use in a clinical cohort of 17 men receiving high dose irbesartan starting on postoperative day 1 and continuing daily, significantly higher IIEF-5 scores were observed at 12 months after nerve-sparing RP compared with a contemporaneous untreated group (45). This pilot investigation obviously requires further confirmation, applying a prospective controlled study design to demonstrate erection rehabilitative benefit of ARB therapy.

### **Prescription for improving erectile function recovery**

A review of this topic in the literature indicates that multiple authorities support the practice of erection rehabilitation after RP (46,47). However, the schemes for rehabilitation are as diverse as there are practitioners of this endeavor. As this presentation attests, no single strategy is uniformly accepted, and the clinical evidence in support of any particular strategy is relatively lacking. This situation makes it difficult to prescribe a rehabilitative therapy or strategy that is likely to be successful in advancing the promptness or vigor of EF recovery. Nevertheless, given the impact of the problem of ED after RP and the quest to improve EF recovery in this setting, some manner of proceeding with practical management is quite desirable at this time.

Some guiding principles for managing ED after RP can be suggested. The management of the problem is broadly conceptualized as interventions for optimizing EF recovery (erection rehabilitation) and interventions for treating ED. Both can be pursued concomitantly with specific and distinct goals, despite the fact that they may involve the same therapy. For example, VED therapy (or whatever alternative) can be used with the premise that it promotes erectile mechanisms or preserve erectile tissue health in conjunction with its mode for eliciting an erection response on-demand for sexual intercourse.

Beyond differentiating management purposes for the occurrence of ED after RP, it is incumbent upon the practitioner to counsel the patient regarding the known risk that ED occurs at least temporarily in the setting of RP. Setting expectations and providing proper education surrounding the reality and circumstances of ED after RP (e.g., risk factors and natural history of EF loss and possible recovery) along with that of all other surgical complication risks are necessary actions to prepare all patients for life after RP. As part of this dialogue, the practitioner should assess the patient's motivations toward retaining sexual function after RP. Patients may vary in their interest to be sexually active, which accordingly influences their compliance with therapeutic protocols after surgery. A gauge of the patient's preoperative level of sexual interest and function is a critical component of this assessment, and the use of diagnostic assessment tools of EF for understanding and documenting EF status before surgery is essential.

Elements of communication and partnering with the patient who is undergoing RP regarding possible EF loss constitute more than just a one-time preoperative activity.

The management of ED after RP, either in accordance with goals of rehabilitation or treatment, must involve coaching and monitoring of functional progress postoperatively. The administration of this support may come from the surgeon directly or other personnel collaborating in the postoperative care of the patient. The timing of this support may be early postoperatively with intensive training and initiation of therapies and it may continue later for many months postoperatively with reevaluation and resetting of therapeutic goals. Conceivably, early and ongoing sexual health intervention is valuable for many patients for the best continuity of care and maintenance of confidence in the therapeutic alliance. It may also fit particularly with goals of erection rehabilitation, in which the early if not preemptive initiation of therapy theoretically reduces derangements of the erectile tissue and mechanisms of erection incurred by RP.

Decisions regarding the best interventions to implement may best derive from a forthright yet uncomplicated discussion of the rationale, likelihood of success, technical requirements, risks and financial costs of a particular therapy. It seems most appropriate to present the scope of considerations of therapy for properly informed implementation by the patient.

For the purpose of erection rehabilitation, in light of the current indefiniteness of therapy as discussed herein, the practitioner may move forward in the motivated patient to initiate an intervention with a therapeutic scheme that is feasible to the practitioner and acceptable to the patient. In the example of PDE5 inhibitors, the practitioner may recommend regular dosing acknowledging that the strength of evidence of efficacy for this therapy is based mainly on preclinical investigation; and given the relative convenience and safety of this therapy the patient may accept this recommendation despite the expense and uncertainty of clinical efficacy. A similar analysis and action plan may be used for any other ED-specific therapy or upcoming innovative therapy designed for EF recovery as well. It is foreseeable that any option that is convenient, tolerable, safe, relatively inexpensive and biologically plausible will be employed for erection rehabilitative therapy at least in the near future.

For the purpose of ED treatment, which serves to induce penile erection when desired, therapy is appropriate at any time after RP in the patient experiencing ED. The course of action would follow precepts for conventional ED treatment (i.e., advancing options successively from lesser to greater invasiveness, a la "process of care" for ED presentations) (10). ED treatment options that are reversible (i.e., oral and

locally self-administered penile therapies) can be expected not to hinder the potential for natural EF recovery, distinct from “irreversible” therapy such as penile prosthesis surgery. Reversible options would ideally be offered for the patient possessing intact erections preoperatively who was able to undergo nerve-sparing RP and has favorable risk factors for regaining natural EF in time after RP.

It is also possible to perform different therapies representing erection rehabilitation and ED treatment concomitantly. This school-of-thought for post-RP management, in fact, may be most ideal for maintenance of uninterrupted sexual activity: erectile ability with assistance as needed with enhancement of natural EF recovery. An example would be combining a regimen of oral therapy using a PDE5 inhibitor or ARB with on-demand use of intracavernosal pharmacotherapy or VED therapy. In time, the requirement for on-demand treatments may lessen upon natural EF recovery and the lesser invasive, convenient therapeutic options may or may not be continued depending upon long-term projections of EF integrity.

### Forward perspective

Despite the certainty of support brought to the concept of erection rehabilitation, far less is certain about the best strategy for carrying out this practice. Continued investigation into the pathophysiologic derangements associated with ED after RP and additionally advancement of scientifically targeted treatments are imperatives for this field of endeavor. Current work in the field is encouraging and testifies to the earnestness of investigators to address the problem. Not unexpectedly, ED-specific therapies have been brought forward initially for this purpose, although their applicability is assuredly better gauged by how well they restore or prevent the loss of erection mechanisms rather than by their erectogenic effects alone. The challenge is to investigate and establish the effectiveness of these therapies as much as that for innovative, up-and-coming interventions with respect to their EF restorative and preventative roles. Predictably in time, treatments will be developed beyond the current armamentarium of indefinitely effective options to options that are truly effective. Clinical availability and tolerability will not suffice as primary criteria for acceptance of any particular therapy, and these variables will be minimally expected of all therapies. It is also anticipated that combination therapies will be used in accordance with a likely multifactorial etiology for ED after RP. Presumably, the best scheme of therapy for EF preservation following

RP will require proficiently performed anatomic nerve-sparing RP when indicated coupled with health and physical fitness optimization by the patient, to which are added multimodal pathophysiology-specific clinical interventions.

Several specific therapeutic prospects carry high interest for erection rehabilitation purposes in the future. Forms of intervention may include not just familiarly used pharmacotherapies, but also growth factor therapies, gene therapy, tissue engineering, stem cell therapy, and possibly local energy-based technologies, any of which may be smartly applied before or possibly in the course of RP surgery aiming for maximal therapeutic benefit. In this article, several novel therapies were mentioned, including statins, erythropoietin and ARBs. Further development and implementation of these promising agents and other technologies are eagerly anticipated, although it is well acknowledged that great effort and expense are associated with their establishment at a standardized level of scientific rigor: randomized, placebo-controlled clinical trial study design. Other touted erection rehabilitative pharmacotherapeutic options have garnered interest in the recent past but have not shown early success at least in the formulations and dosages thus far investigated, e.g., corticosteroids, immunophilin ligands (18,48). Further definition of these agents, which have held such promise at preclinical levels as well as others that have only been investigated at preclinical levels, e.g., rho kinase inhibitors, is encouraged.

### Summary

ED after RP represents the last major frontier of functional recovery outcome concerns following this surgery. A charge presently exists to address this unresolved problem, despite modern improvements in the technical prowess of this surgery. ED management in this setting encompasses a spectrum of interventions meeting goals of immediate erection attainment (ED therapy) and preservation of normal erection ability/enhancement of EF recovery (erection rehabilitation). The latter assignment distinctly specifies the ability to achieve erection responses with stimulation naturally in the absence of erectile aids. Although great effort has been given to develop and implement therapies in this regard, no definite evidence presently supports the effectiveness of a particular pharmacologic therapy or technology for hastening or intensifying EF recovery after RP. However, meaningful evaluations have been undertaken to address this problem,

which in turn have yielded a rational basis for responsible action in today's clinical practice. Scientific studies in the field, both now and in the future, can be expected to usher in effective biomedically valid therapies that will fit with this integrative approach.

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