**Vacuum therapy in penile rehabilitation after radical prostatectomy: review of hemodynamic and antihypoxic evidence**

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Generally, hypoxia is a normal physiological condition in the flaccid penis, which is interrupted by regular nocturnal erections in men with normal erectile function.1 Lack of spontaneous and nocturnal erections after radical prostatectomy due to neuropraxia results in persistent hypoxia of cavernosal tissue, which leads to apoptosis and degeneration of cavernosal smooth muscle fibers. Therefore, overcoming hypoxia is believed to play a crucial role during neuropraxia. The use of a vacuum erectile device (VED) in penile rehabilitation is reportedly effective and may prevent loss of penile length. The corporal blood after VED use is increased and consists of both arterial and venous blood, as revealed by color Doppler sonography and blood gas analysis. A similar phenomenon was observed in negative pressure wound therapy (NPWT). However, NPWT employs a lower negative pressure than VED, and a hypoperfused zone, which increases in response to negative pressure adjacent to the wound edge, was observed. Nonetheless, questions regarding ideal subatmospheric pressure levels, modes of action, and therapeutic duration of VED remain unanswered. Moreover, it remains unclear whether a hypoperfused zone or PO2 gradient appears in the penis during VED therapy. To optimize a clinical VED protocol in penile rehabilitation, further research on the mechanism of VED, especially real-time PO2 measurements in different parts of the penis, should be performed.

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**INTRODUCTION**

Most of the time, the penis is in the flaccid state with very low oxygen tension (PO2 = 25–40 mmHg) in men with normal erectile function.1 However, during nocturnal erectile episodes (occurring 3–5 times per night, each lasting 30–45 min, i.e., a total of 1.5–3 h),2 PO2 is increased in the corpus cavernosum (90–100 mmHg), which provide substantially higher levels of oxygenation; and substances favored by a higher oxygen tension, such as prostaglandin-E1 and nitric oxide (NO), significantly suppress the expression of transforming growth factor-beta 1 (TGF-β1), thereby preventing collagen synthesis and fibrosis.1,3 Spontaneous nocturnal erections are impaired in men who have undergone radical prostatectomy (RP), which leads to persistent hypoxia of cavernosal tissue, resulting in apoptosis and degeneration of cavernosal smooth muscle fibers. Erectile dysfunction (ED) is unavoidable even after the most meticulous nerve-sparing dissection because of the close anatomical proximity of the cavernous nerves to the prostate gland. Recovery of the damaged nerves is a slow process, lasting as long as 3 years, until full return to a new baseline. Therefore, overcoming hypoxia to preserve EF and prevention of structural changes are believed to play a crucial role during neuropraxia.4,5 In 1997, Montorsi *et al.*6 first reported that patients treated with intracavernosal alprostadil had significantly higher rates of spontaneous erections than those who received no treatment after RP (67% vs 20%). This landmark study generated a great deal of interest and enthusiasm in the field of early penile rehabilitation (PR) after RP.

The purpose of PR is to preserve health and minimize damage to erectile tissue during the period of neural recovery by providing adequate oxygenation to the cavernous tissues.1 Even though there is currently no consensus on an optimal protocol, PR is widely applied in clinical practice. Currently, PR methods include the use of phosphodiesterase type 5 inhibitor (PDE5I), vacuum erectile device (VED), intracavernosal self-injection (ICI)/intrarethral suppositories, or a combination of these methods.4,7

**BENEFITS OF VACUUM THERAPY IN PENILE REHABILITATION**

Vacuum therapy utilizes negative pressure to distend the corporal sinoids, thereby increasing infusion of blood to the penis. It was initially utilized for ED with a constriction ring around the base of the penis, which is referred to as a vacuum constriction device (VCD), to maintain an artificial erection for vaginal intercourse. Vacuum therapy is currently the only nonpharmacological, noninvasive strategy for ED, and its effectiveness has been established for various pathogeneses of ED.7 The first commercial VCD received approval from the US Food and Drug Administration (FDA) in 1982,7 and in 1996, it has been

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recommended as one of the three treatment alternatives for organic ED by the American Urological Association (AUA).10

Over the last decade, vacuum therapy using as VED has been investigated as a treatment option for PR after RP without the constriction ring unless for sexual intercourse on demand. There has been growing evidence to support VED as a standard of care in penile rehabilitation early after RP.11 The latest PR trials using VED are summarized in Table 1. Zippe et al.12 first reported an 80% compliance rate (60/74) of VED daily used after PR. 55% (19/60) of patients who daily used VED after 9 months resulted in the natural erection, with 10 of these 19 patients having erections sufficient for vaginal penetration. Raina et al.13 reported the outcomes of 109 patients randomized to daily use of a VED (n = 74) or observation (n = 35). In the VED group, 80% of patients successfully used a VED with a constriction ring for vaginal intercourse. Patients reported improved EF after using VED with significant improvements in mean International Index of Erectile Function-5 (IIEF-5) score and eventual return of natural erections sufficient for vaginal intercourse. Of the 60 successful users, only 23% reported a decrease in penile length and girth compared with 60% of those in the control group. Coincidently, Dalkin and Christopher14 observed 39 men with good preoperative EF who underwent nerve-sparing RP (NSRP) and reported that only 3% of men using a VED for >50% of possible days had a decrease in stretched flaccid penile length of >1 cm, as compared to 48% in previous reports. The authors concluded that early VED use facilitated resumption of sexual activity and preserved penile length. Kohler et al.15 reported significantly higher IIEF-5 scores in the VED treatment group (17/28) than the control group (11/28) at 3 and 6 months after RP. When evaluating penile shortening, the mean penile length loss at 3 and 6 months was 1.87 cm and 1.82 cm, respectively, in the control group, whereas no significant changes were observed in the VED group.

The combined use of a VED and PDE5I or ICI showed some synergistic effects on refractory ED after RP. Raina et al.16 prescribed 100 mg of sildenafil to 31 patients who were unsatisfied with early use of a VCD alone after RP 1 to 2 h before VCD use for sexual intercourse. Of these patients, 24 (77%) reported improved penile rigidity and sexual satisfaction with significantly increased penile rigidity scores. Among seven men who reported return of natural erections, five reported erections sufficient for vaginal penetration.16 The same team reported long-term potency of 141 sexually active patients who underwent RP. At 5 years, 62% remained sexually active, of whom 71% had natural erections sufficient for intercourse, 8.5% were still using sildenafil, and 10% were using combination therapy of sildenafil plus a VED. Of the 113 sexually active patients at 1 year, 50 (44%) had a return of spontaneous erections, of whom almost 60% (30) tried early VED and had better compliance, efficacy, and fewer economic constraints.17 A study by Engel18 randomized 23 bilateral nerve-sparing robotic prostatectomy ED patients to receive tadalafil (n = 10) or tadalafil plus VED (n = 13). The combination regimen group had significantly higher IIEF-5 scores and greater penile hardness scores and higher compliance than the monotherapy group. After 12 months, 92% of patients who received the combination therapy were able to engage in vaginal intercourse versus 57% of the tadalafil group.

To explore the molecular mechanism of VED, a rat-specific VED, which simulates human VED, was successfully created and applied on a bilateral cavernous nerve crush (BCNC) rat model by our group.19 Our preliminary data indicated that daily VED therapy significantly improved the intracavernosal pressure/mean artery pressure ratio; decreased hypoxia-inducible factor-1α (HIF-1α) and TGF-β1 levels, collagen deposition, and smooth muscle cells apoptosis; and increased the level of endothelial NO synthase and eNOS-muscle actin.20 Our further research using a consistent approach showed that VED therapy significantly preserved penile length after BCNC and partly reversed BCNC-induced collagen deposition (especially collagen I), smooth muscle apoptosis, and tunica albuginea collagen fiber irregularities in ultrastructural modification.21 Our findings from the animal model were consistent with previous clinical data reported by Lin et al.22 as both studies indicated anti-fibrosis and anti-apoptosis mechanisms of VED.

At present, phosphodiesterase type 5 inhibitors (PDE5-Is) are still the first line therapy for penile rehabilitation after RP. A latest meta-analysis by Li et al.23 included seven randomized placebo-controlled trials with a total of 2655 male patients after RP, showed that PDE5-Is are well-tolerated and are more effective than placebo. Patients in the PDE5-Is group showed significant improvement in the International Index of Erectile Function—Erectile Function domain score, Global Assessment Questionnaire, Sexual Encounter Profile question 2 and 3, with acceptable treatment adverse event. In other hand, animal studies showed PED5I might reduce the hypoxia and structural changes meanwhile improve erectile function through preventing veno-occlusive dysfunction in the penile tissue after cavernous nerve resection. For penile length, a randomized placebo-controlled study by

Table 1: Benefits of vacuum therapy in penile rehabilitation

| Authors            | Year | Patients | Follow-up (months) | Study design | Treatment                                 | Result                                                                 |
|--------------------|------|----------|-------------------|--------------|-------------------------------------------|-----------------------------------------------------------------------|
| Zippe et al.12     | 2001 | 74       | 12                | Prospective  | Daily VED (with or without constriction ring) | High compliance rate (80%) and few complications; encourage early sexual activity and interest in patients (and partners) |
| Raina et al.16     | 2005 | 31       | 4.5               | Prospective  | VCD and sildenafil 100 mg on demand        | Improve sexual satisfaction and penile rigidity in patients unsatisfied with VCD alone |
| Raina et al.13     | 2006 | 109      | 9                 | Prospective, randomized | Daily VED (with or without constriction ring) | Early sexual intercourse, early patient/spousal sexual satisfaction, and potentially an earlier return of natural erections sufficient for vaginal penetration |
| Kohler et al.15    | 2007 | 28       | 9.5               | Prospective, randomized | Daily VED                                     | Improves early sexual function and helps to preserve penile length |
| Dalkin and Christopher14 | 2007 | 42       | 3                 | Prospective  | Daily VED                                     | Only 1/36 (3%) had a decrease in SPL of ≥1.0 cm, while 48% of previous report |
| Raina et al.17     | 2010 | 141      | 1.5 years         | Retrospective | PDE5I, VED                                   | 48.7% (55/113) of sexual active patient were using VED, 60% (30/50) of whom had a return of spontaneous erections tried early VED |
| Engel18            | 2011 | 23       | 12                | Prospective, randomized | Tadalafil versus tadalafil plus VED          | Combination therapy had significantly higher IIEF-5 scores, greater penile hardness scores, higher compliance than the monotherapy group |

VED: vacuum erectile device; VCD: vacuum constriction device; PDE5I: phosphodiesterase type 5 inhibitor; IIEF-5: international index of erectile function-5; SPL: stretched penile length
Montorsi et al. showed the penile length loss was significantly reduced versus placebo in tadalafil once daily group by 4.1 mm ($P = 0.032$). Another study from Beroookhim et al. demonstrated that PDE5I use moderated stretched flaccid penile length loss, with patients who regularly used PDE5I having no loss at 6 months after RP.

The mechanisms and cellular pathways behind the PDE5I effect on post-RP are not fully understood. Most authors believe that PDE5I enhance erectile function by preventing the degradation of cyclic guanosine monophosphate, however, this theory shows the limitation of PDE5I in early use after RP, because the requirement of intact nerves to produce nitric oxide for proper function. There have been theories that PDE5I may work through more complicated cellular mechanisms, including activation of anti-apoptotic and anti-fibrotic factors is still unresolved by robust evidence.

VED is nonpharmacological, noninvasive, and easy to learn how to use. It has many benefits as aforementioned, including preservation of penile length, improved sexual satisfaction of both patients and their partners, and promotion of the earlier return of spontaneous erections. Patients may maintain sufficient artificial erection for vaginal intercourse using the constriction ring on demand. Currently, VED therapy is the second most commonly used modality for PR in a recent survey of AUA members. Given its low complication rate, relatively high compliance rate, and independence from the NO pathway, VED is an ideal modality in PR immediately after RP. However, the mechanisms of VED in PR and the exact hemodynamic changes in the penis during VED therapy are not well-known.

Despite FDA approval in 2006 for PR after RP, there have been no large multicenter randomized controlled trials of VED as a rehabilitation strategy; thus, further studies to explore the underlying mechanisms of VED therapy after RP are warranted.

**Table 2: Penile hemodynamic and blood oxygen supply changes during vacuum therapy**

| Authors          | Year | Object  | Measurement                        | Result                                                                 |
|------------------|------|---------|------------------------------------|------------------------------------------------------------------------|
| Diederichs et al. | 1989 | Primates| Intracavernous pressure            | Subatmospheric pressure induces an expansion of the penis followed by increased blood inflow |
| Broderick et al.  | 1992 | Patients| Color Doppler                      | Vacuum transiently increased cavernous arterial blood flow velocity; arterial inflow was diminished once the constraining band used |
| Donatucci and Lue | 1992 | ED      | Color Doppler                      | Chronic VED usage increases cavernous arterial flow                      |
| Bosshardt et al.  | 1995 | ED      | Rigiscan monitor Blood gas analysis| The average rigidity was >80%; SO$_2$ of corporal blood was 79.2% (58% arterial and 42% venous) immediately and ischemia after 30 min after VED application |
| Yuan et al.       | 2009 | Rat     | Observation                        | Penis became engorged, changing color from red to dark red, during a treatment cycle lasting 5 min |
| Yuan et al.       | 2010 | BCNC rat| Immunohistochemistry               | VED therapy partially reversed HIF-1a expression induced by BCNC          |
| Lin et al.        | 2013 | BCNC rat| Blood gas analysis                 | Significant increase in mean SO$_2$ by VED application compared with the flaccid and traction groups (62% arterial and 38% venous) |
| Welhiver et al.   | 2014 | Patients after RP | Oximeter                   | SO$_2$ for both the glans and corpora significantly increased over baseline (pre-VED use) levels at all time-points (0, 5, 15, 30, and 60 min after VED) |

ED: erectile dysfunction; VED: vacuum erectile device; BCNC: bilateral cavernous nerve crush; HIF-1a: hypoxia-inducible factor-1a; RP: radical prostatectomy
5 min. Our previous data demonstrated that VED therapy partially reversed HIF-1α expression induced by BCNC. In 2013, Lin et al. applied the same rat-specific VED on BCNC rats and confirmed our findings that VED therapy was effective in the prevention of BCNC-induced penile shrinkage. For cavernous oxygen saturation, the authors reported a significant increase in mean SO2 by VED application compared with the flaccid and traction groups (88.25% vs 76.53% and 78.93%, respectively; P < 0.05). The calculated blood composition in the corpus cavernosum immediately after VED application was 62% arterial and 38% venous. Very recently, Welliver et al. conducted a pilot study to determine penile oxygen saturation before and after VT in patients with ED after RP. The oximeter was placed at the thigh, corpora, and glans penis; and tissue oxygen saturation was measured before VED use, immediately afterward, and then repeated at 5, 15, 30, and 60 min after removal of VED. Oxygen saturation for both the glans corpora significantly increased (55%) over baseline (pre-VED use) levels at all time-points. These increases were statistically significant for the entirety of the study when compared with baseline values, even 60 min after VED use.

**DISCUSSION**

Azadzoi et al. investigated the hemodynamics of penile erection by measuring oxygen tension as an indicator of arterial blood flow. Their observations provided physiological evidence of an important subcutaneous circulation that carried most of the intracavernosal blood flow into the flaccid penis. Deep intracavernosal blood flow significantly increased, consistent with both venous and arterial blood with pelvic nerve stimulation. However, an artificial erection induced by injection of vasoactive drugs appeared to depend more on intracavernosal shunting of blood than on increased total arterial blood flow to the penis. Fraiman et al. found that denervated muscular atrophy was most apparent during the first 4–8 months after RP. PDE5I may be insufficient to relax the contractile penile smooth muscle to acquire erection during the period of neurapraxia, as it requires intact nerves to produce neuronal NO. Nevertheless, VED therapy is likely the only method that can actually overcome RP-induced hypoxia in the consistently flaccid penis soon after RP, and it is recommended for patients immediately after catheter removal. Traditionally, patients should leave the penis fully engorged inside the pump for 5 min and repeat for another 5 min after a 1–2–min interval with the penis totally flaccid. We observed that the color of penile glans gradually changed from red to dark red over a period of 5 min. Until now, the therapy protocol of the 5–1–5-min action mode was empirical, as there was no support by scientific evidence based on clinical or basic data.

Besides VED, negative pressure is wildly used in wound healing, and practitioners of traditional Chinese medicine used fire-cupping to cure abscesses 1700 years ago. As an adjuvant approach of acupuncture and moxibustion, fire-cupping can increase topical blood supply and promote wound healing. During the last 50 years, increasing evidence has indicated that certain wounds respond to subatmospheric pressure in a porcine model. Nonetheless, whether a similar mechanism of the 5–1–5-min action mode was empirical, as there was no support by scientific evidence based on clinical or basic data.

In a study utilizing a pig model to determine the effects of subatmospheric pressure on laser Doppler-measured blood flow in the wound and adjacent tissue, Morykwas et al. reported a four-fold increase in blood supply, as compared to baseline values, under a continuous negative subatmospheric pressure of 125 mmHg. Moreover, Chen et al. found that vacuum-assisted closure (VAC) promoted capillary blood flow velocity, increased capillary diameter and blood volume, stimulated endothelial closure (VAC) promoted capillary blood flow velocity, increased capillary diameter and blood volume, stimulated endothelial proliferation and angiogenesis, narrowed endothelial spaces, and restored the integrity of the capillary basement membrane. Petzina et al. reported a decrease in parasternal wound edge microvascular blood flow when the left internal mammary artery was removed in a porcine sternotomy wound model. However, VAC therapy stimulates blood flow even after harvesting of the internal mammary arteries. Wackenfors et al. measured microvascular blood flow considering different tissue types and distance from the wound edge in a pig sternotomy model after application of VAC. They reported an increase in both the hyperperfused zone and negative pressure immediately adjacent to the wound edge. Compared to subcutaneous tissue, the increase in blood flow occurred closer to the wound edge in muscular tissue. Lindstedt and Hlebowicz observed that NPWT of the open abdomen induced ischemia in the small intestinal loop and the omentum lying in close contact with the visceral protective layer, and that the degree of ischemia seemed to increase with increasing negative pressure. This group also reported that myocardial topical negative pressure (TNP) of ~50 mmHg significantly increased microvascular blood flow in the underlying myocardium in normal, ischemic, and reperfused porcine models, as measured by laser Doppler velocimetry. Their further research showed that TNP between ~75 and ~150 mmHg did not significantly increase microvascular blood flow in normal or ischemic myocardium. Different from wound healing, hypoperfusion was not produced in the epicardium during the application of myocardial topical negative pressure in a porcine model.

The mechanisms of how NPWT affects blood flow in the wound edge are also only partly known. The superficial and deep portions of the wound bed are subjected to compression and traction forces, respectively. While tissue traction promotes widening of blood vessels, thereby inducing hyperfusion, tissue compression has the opposite effect and results in hypoperfusion. Both of these hemodynamic alterations contribute to wound healing as deep tissue hyperfusion enhances oxygen and nutrient delivery, whereas superficial tissue hypoperfusion and ensuing hypoxia lead to the formation of a gradient of vascular endothelial growth factor, which favors angiogenesis. On the other hand, microdeformations enhance cellular proliferation and myofibroblast differentiation. Therefore, the presence of mechanical stress itself and TGF-β1 activation appear to be critical to NPWT-induced myofibroblast differentiation. The role of myofibroblasts in wound contraction and extracellular matrix deposition is well-established. Myofibroblasts also appear to be important actors in vessel translocation and angiogenesis, a process by which neovascularization occurs during wound healing.

The hypoperfused zone is believed to play an important role in tissue fibrosis, which is consistent with the observed pathophysiological changes in cavernosal tissue after RP. However, as mentioned above, the extent of hypoperfused zones varies in different tissues and among negative pressure levels. Moreover, researchers failed to observe hypoperfusion produced in myocardial tissue by topical negative pressure in a porcine model. Nonetheless, whether a similar hypoperfused zone is present in the penis during VED therapy remains unknown. Moreover, previous studies have only considered blood...
and oxygen delivery to the corpus cavernosum distributed uniformly, but this has not been evaluated in VED therapy. Pressure in the cylinder gradually declined from normal atmosphere to negative level (−150 to −200 mmHg), although the duration of this period may differ with the use of single-handed devices, as opposed to battery-operated vacuum pumps. According to a previous study, venous blood flowed to the cavernous tissue before arterial dilatation under traction force in this procedure. Oxygen content, which is lower in the initial inflowed venous blood, will be consumed in the distal penis, leading to a hypoxic state earlier than the base of the penis. Therefore, we hypothesize that there exists a gradual decrease in PO2 in the whole corpus cavernosum during VED therapy.

CONCLUSION
Consistent with the increase in blood supply and high tissue PO2 under NPWT, color Doppler and blood gas analysis revealed that VED therapy increased the infusion of both arterial and venous blood. However, questions about ideal subatmospheric pressure levels, mode of action, and therapeutic duration remain unanswered. Furthermore, whether a hyperperfused zone and PO2 gradient exist in the penis during VED therapy remains unclear. To optimize the PR regimen, further research on the mechanism of VED, especially real-time PO2 in different parts of the penis, should be performed.

AUTHOR CONTRIBUTIONS
SQ and LG searched and collected the literature, SQ drafted the manuscript. JY and QW designed and modified the manuscript and JY finalized and approved the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declare no competing interests.

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