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REVIEW

Sexual Function

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 PO_2 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 PO_2 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 (PO_2 = 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] PO_2 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.[4–7] In 1997, Montorsi *et al*.[8] 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.[5] 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)/intraurethral 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 sinusoids, 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,[9] 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 RP. 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 Christopher[14] 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 Engel[18] 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 crash (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 α-smooth 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 Christopher[14]	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
Engel[18]	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.[24] showed the penile length loss was significantly reduced versus placebo in tadalafil once daily group by 4.1mm ($P = 0.032$). Another study from Berookhim et al.[25] 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.[26] 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 unproven by robust evidence.[7,27]

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.[4,7] Patients may maintain sufficient artificial erection for vaginal intercourse using the constriction ring on demand.[4,6,11] Currently, VED therapy is the second most commonly used modality for PR in a recent survey of AUA members.[28] 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.[7,20] Despite FDA approval in 2006 for PR after RP, there have been no large multicenter randomized controlled trials of VED as a rehabilitation strategy;[29] thus, further studies to explore the underlying mechanisms of VED therapy after RP are warranted.

PENILE HEMODYNAMIC AND BLOOD OXYGEN SUPPLY CHANGES DURING VACUUM THERAPY

Numerous studies have explored changes in penile hemodynamics and oxygen supply caused by vacuum therapy; they indicated that the beneficial effects of VED therapy were related to antihypoxia by increasing cavernous infusion and tissue blood PO_2; **Table 2** summarizes the clinical and basic research evidence. However, due to technical limitations, real-time changes of PO_2 in cavernous tissue during VED therapy have not been elucidated.

A previous study showed that there is a vasodilatory effect on the arteries of the forearm in volunteers exposed to a subatmospheric pressure of −150 to −200 mmHg, which is similar to the pressure used in VED.[30] Diederichs et al.[31] observed a decrease in intracavernous pressure within 1–3 s after applying negative pressure in primates. Following a gradual increase in blood flow to corpus cavernosum, intracavernous pressure recovered to 50% after 17 s and to 100% by 30–60 s. The authors speculated that vacuum-induced penile tumescence is a passive procedure that occurs without smooth muscle relaxation or release of neurotransmitters. In addition, they noticed an increase in intracavernous pressure from suction with a partially constricting rubber, similar to that after intracavernous papaverine injection.

Using color Doppler ultrasound, Broderick et al.[32] showed that negative pressure transiently increased central cavernous arterial blood flow velocity. After applying a constricting band, the cross-sectional area of the cavernous body doubled. The constriction ring was placed at the base of the penis to prevent venous outflow in order to maintain an artificial erection; however, color Doppler showed no arterial inflow into the penis after the placement of a constriction ring. A study by Donatucci and Lue[33] further indicated that chronic VED usage increased cavernous arterial flow in men with mild vasculogenic ED. These data suggested that the erectile state maintained distal to VCD was associated with low flow and relatively ischemic. Actually, compared with naturally occurring erections, an "artificial erection" appears discolored (dusky) and feels cooler than normal, with increased distal volume, especially at the glans penis, and the patient may complain of numbness and pain.[9] These findings indicated a risk of ischemia when a constriction ring is applied to maintain an erection.

In a study of 30 impotent men, Bosshardt et al.[34] showed that 26/26 of the participants who used a VCD for 6 months were able to engage in sexual intercourse. Patients also reported significant improvements in spontaneous morning erections. The authors performed blood gas analysis before and immediately after the application of VCD, and repeated blood gas analysis 15 and 30 min later with the constriction ring in place. The mean O_2 saturation of corporal blood immediately after VCD-induced erection was 79.2%, and the calculated contribution of arterial and venous blood to penile blood volume was 58% and 42%, respectively. The 30-min blood gas analysis also showed hypoxia of penile blood. This article led to the recommendation that to prevent ischemic injury to the penis, a constriction ring should not be left on for >30 min and should be avoided in PR unless the patient is planning vaginal intercourse.

In our earlier study,[19] we observed that the penis became engorged, changing color from red to dark red, during a treatment cycle lasting

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

Authors	Year	Object	Measurement	Result
Diederichs et al.[31]	1989	Primates	Intracavernous pressure	Subatmospheric pressure induces an expansion of the penis followed by increased blood inflow
Broderick et al.[32]	1992	Patients	Color Doppler	Vacuum transiently increased cavernous arterial blood flow velocity; arterial inflow was diminished once the constricting band used
Donatucci and Lue[33]	1992	ED patients	Color Doppler	Chronic VED usage increases cavernous arterial flow
Bosshardt et al.[34]	1995	ED patients	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.[19]	2009	Rat	Observation	Penis became engorged, changing color from red to dark red, during a treatment cycle lasting 5 min
Yuan et al.[20]	2010	BCNC rat	Immunohistochemistry	VED therapy partially reversed HIF-1α expression induced by BCNC
Lin et al.[22]	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)
Welliver et al.[29]	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 crash; HIF-1α: hypoxia-inducible factor-1α; RP: radical prostatectomy

5 min. Our previous data demonstrated that VED therapy partially reversed HIF-1a expression induced by BCNC.[20] In 2013, Lin *et al*.[22] 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 SO_2 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.[22] Very recently, Welliver *et al*.[29] 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 and 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.[29]

DISCUSSION

Azadzoi *et al*.[35] 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 subtunical 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.[35] Fraiman *et al*.[36] found that denervated muscular atrophy was most apparent during the first 4–8 months after RP. PDE5I may be insufficient to relax the contractive 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.[37] 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.[14] We observed that the color of penis glans gradually changed from red to dark red over a period of 5 min.[19] 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.[38] 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 within a closed dynamic delivery system. However, the mechanisms of negative pressure wound therapy (NPWT) remain unclear; proposed mechanisms include increased blood flow, decreased edema, cytokine release induced by mechanical stretching, and increased lactate and oxygen tension in the tissue with induction of collagen transcription and angiogenesis.[39] A series of basic animal studies to explore changes in hemodynamics and blood supply under subatmospheric pressure in wound healing have indicated that NPWT may improve the delivery of oxygen and nutrients to wound tissue and accelerate waste removal by inducing a large increase in blood flow.

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*.[40] 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*.[41] found that vacuum-assisted 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*.[42] 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*.[43] 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 hypoperfused 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[44] 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.[45] Different from wound healing, hypoperfusion was not produced in the epicardium during the application of myocardial topical negative pressure in a porcine model.[46]

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.[47] While tissue traction promotes widening of blood vessels, thereby inducing hyperperfusion, tissue compression has the opposite effect and results in hypoperfusion.[48] Both of these hemodynamic alterations contribute to wound healing as deep tissue hyperperfusion 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.[48,49] 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.[50,51] 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.[52]

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,[30] venous blood flowed to the cavernosum tissue before artery dilation 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 PO_2 in the whole corpus cavernosum during VED therapy.

CONCLUSION

Consistent with the increase in blood supply and high tissue PO_2 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 hypoperfused zone and PO_2 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 PO_2 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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