

# Penile Oxygen Saturation in the Flaccid and Erect Penis in Men With and Without Erectile Dysfunction

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**ABSTRACT:** It is believed that a chronic state of corporal oxygen desaturation or hypoxemia secondary to the loss of nocturnal erections is a fundamental pathophysiological cause of erectile dysfunction (ED). Limited invasive blood gas measurements in human models have shown decreased oxygen tension in vasculogenic impotence. Normative data on flaccid and erect oxygen saturation (StO<sub>2</sub>) levels are lacking due to the invasive nature of blood gas determinations. Our objective was to determine StO<sub>2</sub> in the flaccid and erect penis in men with and without ED using a tissue oximeter. This FDA-approved instrument provides instantaneous, noninvasive, painless local tissue StO<sub>2</sub> measurements, which highly correlate to blood gas data. The study population included 171 men (18–90 years) who presented to one andrologist. They completed the Sexual Health Inventory for Men (SHIM) based on pharmaco-

logically unassisted erectile function and had penile StO<sub>2</sub> measurements taken. 64 of these men had repeat measurements after PGE-1 induced erections. There are significant differences ( $P < .001$ ) in corporal and glanular StO<sub>2</sub> in the flaccid (right corpora, 45.23%; left corpora, 52.50%) and erect state (right corpora, 76.58; left corpora, 80.42). Men with ED (right corpora, 45.04% vs 53.58%;  $P = .02$ ; and left corpora, 50.95% vs 58.78%;  $P = .03$ ) have significantly lower corporal penile StO<sub>2</sub>. Future prospective data collection can correlate penile StO<sub>2</sub> in specific populations, such as diabetics and RRP patients. This may help further elucidate the relationship between corporal hypoxia and the development and progression of ED and possibly its treatment and prevention.

Key words: Corporal oxygen saturation, tissue oximeter.

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The local mechanisms and peripheral control of penile erections and detumescence have been extensively studied. These complex events require intact vascular structure, smooth muscle, endothelium, and nerves. Smooth muscle fibers of the corpora cavernosa and penile arteries relax following a reduction of intracellular calcium. This relaxation causes an increase of blood flow to the penis and sinusoid spaces. Intracellular mediators (cyclic nucleotides, cAMP, and cGMP) regulate these intracellular calcium movements, and gap junctions facilitate rapid ion exchange between the smooth muscle fibers. This makes the erectile tissue a functional syncytium. Parasympathetic neurons in cavernous nerves synthesize nonadrenergic, noncholinergic neurotransmitters, mainly nitric oxide (NO), which acts on smooth muscle fibers. NO crosses into the smooth muscle cell and reacts with guanylate cyclase, catalyzing the conversion of GTP to GMP. NO increases intracellular cGMP, which leads to

smooth muscle relaxation and the initiation of an erection.

Oxygenation of the cavernous tissue is important in regulation of local mechanisms of erection. Blood flow arterialization during erections is felt to be crucial in providing the free oxygen necessary for formation of NO by neuronal and endothelial nitric oxide synthase. Low oxygen tension inhibits NO synthetase activity and the release of NO in penile corpus cavernosum regardless of the normal or physiological state of the nerves and endothelium. The lack of free oxygen, transported to the penis by hemoglobin, is theoretically detrimental to the synthesis of NO and cGMP formation. Corporal hypoxia predisposes to cavernous fibrosis from the increased synthesis of collagen via TGF beta, resulting in erectile dysfunction (ED).

Limited invasive blood gas studies in human models have shown decreased oxygen tension in vasculogenic impotence and a hypoxic cavernosal state in the flaccid penis. Kim et al (1993, 1996) showed that isolated human and rabbit corpus cavernosum tissue strips exposed to arterial-like partial pressure of oxygen (pO<sub>2</sub>) relaxed with acetylcholine and to electrical stimulation of the autonomic dilator nerves. Decreasing pO<sub>2</sub> to levels measured in the flaccid penis resulted in loss of the relaxation responses. Normoxic conditions readily restored endothelium-dependent and neurogenic relaxation. In the rabbit corpus cavernosum, low pO<sub>2</sub>

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reduced basal levels of cGMP and prevented cGMP accumulation induced by stimulation of dilator nerves. Furthermore, low pO<sub>2</sub> inhibited nitric oxide synthase activity in corpus cavernosum cytosol. It was concluded that physiological concentrations of oxygen modulate penile erection by regulating nitric oxide synthesis in corpus cavernosum tissue (Kim et al, 1993, 1996).

One theory is that progressive erectile dysfunction occurs due to the loss of rapid eye movement (REM) nocturnal penile tumescence (NPT). Whereas men without ED will demonstrate erectile activity for as much as 60% of their sleep time, men with ED have been shown to lose NPT. This loss of NPT occurs with numerous pathologic processes. This is seen with aging and in disease states, such as diabetes, hypogonadism, and radical pelvic surgery (Karacan et al, 1978, 1989). A dramatic loss of NPT is seen after a radical prostatectomy, due to denervation or nerve damage (McCullough, 2001; Padma-Nathan et al, 2004). Penile shrinkage, muscular atrophy, and associated penile tissue apoptosis and fibrosis have been documented in the animal model and in humans after cavernous nerve damage (Klein et al, 1997; Fraiman et al, 1999; User et al, 2003; Schwartz et al, 2004). The chronically flaccid state theoretically results in a chronic state of penile hypoxia.

The painful, invasive nature of blood gas determination has limited the accrual of normative data on penile oxygen saturation (StO<sub>2</sub>) levels in the flaccid and erect state in potent men and in men with or without ED. It has never been shown that men with ED have a chronic state of oxygen desaturation or a lower resting oxygen saturation state. The objective of this study was to noninvasively determine the StO<sub>2</sub> levels in men with and without ED in the flaccid and erect states through the use of Optical Diffusion Imaging and Spectroscopy (ODIS) with the ODISsey Tissue Oximeter (Odissey).

## Materials and Methods

Prospective StO<sub>2</sub> levels and retrospective historical data were collected as part of an institutional review board–approved project and were used to analyze a series of 171 patients between the ages of 18 and 90 years. All 171 patients presented to one andrologist. After giving informed consent, they completed the Sexual Health Inventory for Men (SHIM) based on pharmacologically unassisted erectile function and had penile StO<sub>2</sub> measurements taken. Testing was done in conjunction with a previously scheduled office visit. Equipment was provided by ViOptix (Fremont, Calif).

Men undergoing diagnostic/therapeutic MUSE applications or PGE-1 penile injections as part of their treatment had additional StO<sub>2</sub> measurements 10 to 15 minutes after the instillation of vasoactive material. No additional office visits

were planned for measurements. Demographic data including age, race, partner status, comorbidities, surgeries, medications, and endothelial risk factors (diabetes, smoking, hypertension, hyperlipidemia, depression) were recorded.

Penile StO<sub>2</sub> measurements were performed with the use of a tissue oximeter, Odissey (Figure 1). The Odissey is based on optical diffusion infrared spectroscopy, ODIS. ODIS is a patent-protected, noninvasive method of characterizing tissue StO<sub>2</sub> based on measurements of photon scattering and absorption. It is achieved by sending optical signals (continuous wave, pulse, or intensity-modulated wave) into tissue and measuring the corresponding diffuse reflectance or transmittance on the tissue surface. Absorption is caused by interaction with chromophores, which are light-absorbing units of tissue. Hemoglobin is one of the principal chromophores in tissue. Evaluation of reflected light gives clinical information about the biochemical status of these chromophores (Xu et al, 2003).

The Odissey is an FDA-approved instrument providing instantaneous, painless local tissue StO<sub>2</sub> measurements using the ratio of chromophores, oxyhemoglobin (HgbO<sub>2</sub>), and deoxyhemoglobin (Hgb) (Tamura et al, 1990). This system is highly sensitive and specific, with a greater than 98% correlation to blood gas data in vitro and in vivo (Xu et al, 2003). The Odissey is lightweight and user-friendly and utilizes either a hand-held probe for spot readings or a patch for continuous monitoring. Choi used similar technology in the anesthetized rabbit model showing that changes in oxyhemoglobin concentrations and StO<sub>2</sub> correlated with frequency-dependent increases in ICP (Choi et al, 2002).

Each patient had a minimum of 5 measurements taken at 5 sites (right thigh, right corpora, mid-glans, left corpora, left thigh) using the hand-held probe (Figure 2). Thigh measurements were included as controls. A subset of 64 patients had prostaglandin E-1 urethral suppository or injections (PGE<sub>1</sub>) administered, with repeat StO<sub>2</sub> measurements (after 10 minutes) as part of the therapeutic or diagnostic evaluation. The StO<sub>2</sub> per site and the effect of vasoactive substance on penile and thigh oximetry was recorded. The StO<sub>2</sub> recorded for this probe is an average of an approximate volume of 1 cm<sup>3</sup> of tissue beneath the probe, well within the corporal body. The raw data was transferred via infrared port to the investigator's computer, where it was then converted into an Excel spreadsheet in which means and standard deviations were calculated for each measured site. Statistical analysis was performed by using the Student's *t* test and ANOVA with SAS software, JMP 5.1 (Cary, NC).

## Results

The mean age of patients in the study was 58.6 (SD 11.69) years, with a significantly older ED group, 60.79 vs 47.5 years (*P* = .001). Table 1 compares the non-ED (SHIM > 21, *n* = 27) and ED (SHIM < 21, *n* = 144) groups in regards to age, endothelial risk factors, radical retropubic prostatectomy (RRP) status, and SHIM

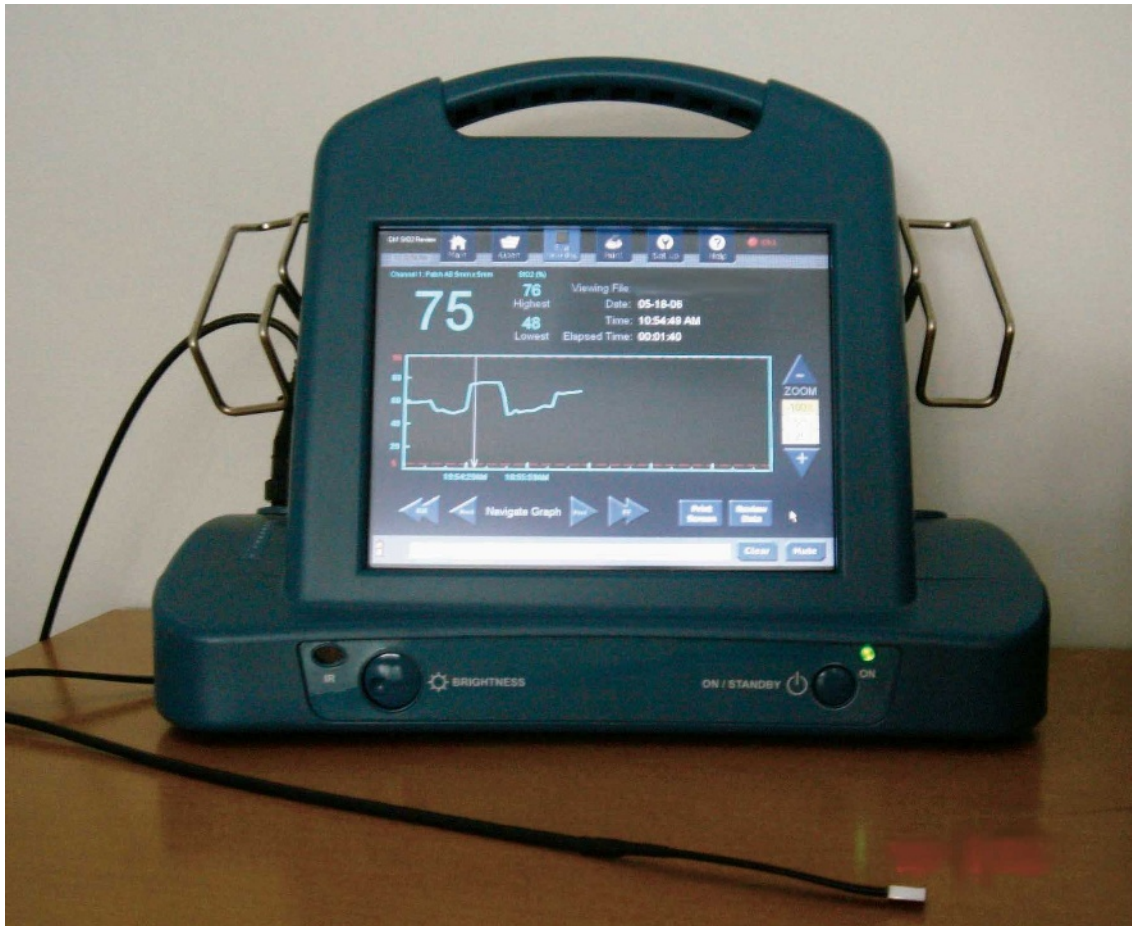


Figure 1. Odissey oximeter.

scores. There is a consistent trend of increased endothelial disease risk factors in men with ED, though the low numbers of non-ED men precluded statistical significance except in hypertension and RRP status. By SHIM scores, 48% of men had severe ED ( $\leq 7$ ), 9% moderate ED (8–14), 27% mild (15–21), and 16% no ED (22–25).

Corporal oxygenation was significantly lower in men with ED than in men with no ED (Table 2). When patients were segregated by ED severity, patients with more severe ED (SHIM  $\leq 7$ ,  $n = 79$ ) had significantly lower corporal flaccid StO<sub>2</sub> than those with no ED (SHIM  $> 21$ ,  $n = 27$ ), though the age was also significantly higher (Table 3). Sixty-seven percent of the men with severe ED had undergone RRP, with a mean time from surgery of 25 months (1–108) and age of 61. Glanular oxygenation was not affected by ED status or age, by categorical or regression analysis. Age appeared to have a significant effect on flaccid corporal StO<sub>2</sub> after age 60. There appeared to be no consistent trend in men younger than 60 (Table 4).

Administration of PGE-1 intracorporally or intraurethally resulted in arterialization of corporal and glanular StO<sub>2</sub> without increases in thigh measurements. Table 5 contains baseline StO<sub>2</sub> measurements for all 171 patients divided into the 5 sites by mean and standard deviation. The pre-PGE<sub>1</sub> StO<sub>2</sub>, postvasoactive StO<sub>2</sub>, and percent of change for the 64 ED patients are also shown in Table 5. There was a significant mean percentage improvement in StO<sub>2</sub> in the ED patients with vasoactive substance in both the corpora and mid-glans sites. Specifically, there is a 150% ( $P < .001$ ) improvement in the right corpora, 105% ( $P < .001$ ) improvement in the left corpora, and 26% ( $P < .001$ ) improvement in the mid-glans following vasoactive administration. PGE<sub>1</sub> had no significant effect on thigh StO<sub>2</sub>. In men receiving MUSE, the improvement in corporal and glanular StO<sub>2</sub> occurred despite the marginal erection. Doses of MUSE used were 125 and 250  $\mu\text{g}$ . The average dose of intracavernosal PGE-1 was less than 10  $\mu\text{g}$  and was always accompanied by a partial or full erection.



Figure 2. Measurement of oximetry on right corpora.

## Discussion

Penile oxygenation is felt to play a critical role in the regulation of local mechanisms of erection. Arterialization of blood flow during nocturnal erections leads to the formation of NO, synthesis of cGMP, and eventual tumescence. Limited human studies have shown that the

Table 1. Demographics, RRP, and SHIM scores of non-ED (SHIM >21) and ED (SHIM <21) patients

	Potent n = 27	Impotent n = 144	P Value
Age	46.24	60.70	.001
Smoking	4	11	.2
Diabetes	0	7.63	.06
Hypertension	8	35.2	.003
Hyperlipidemia	24	37	.18
Coronary artery disease/ peripheral vascular disease	0	6	.08
RRP	4	55	.0001

low  $pO_2$  (venous blood) in intracavernosal blood of the flaccid penis is elevated to arterial  $pO_2$  levels with parasympathetic stimulation or intracavernosal injections. To date, there are limited blood gas measurements for the determination of  $pO_2$ , due to the painful and invasive nature of the technique. There is a paucity of normative data on flaccid and erect  $StO_2$  levels. The Odissey is an optical-based, FDA-approved instrument that is highly sensitive and specific, with greater than

Table 2. Penile and thigh  $StO_2$  of non-ED (SHIM >21) and ED (SHIM ≤ 21) patients

	Potent n = 27	Impotent n = 144	P Value
R thigh	61.15	58.04	.19
R corpora	56.04	44.10	.01
Glans	70.38	73.02	.20
L corpora	58.94	50.16	.01
L thigh	65.49	61.56	.13
SHIM score	24.30	8.0576	.0001

Table 3. Penile and thigh StO<sub>2</sub> in men with severe ED and no ED

	SHIM >21 (SEM) n = 27	SHIM < 7 (SEM) n = 79	
Age	45.65 (1.9)	62.93 (1.09)	0.0001
R thigh	61.84 (2.4)	58.02 (1.33)	0.16
R corpora	53.58 (3.2)	45.04 (1.77)	0.02
Glans	69.78 (1.71)	73.26 (0.92)	0.08
L corpora	58.78 (3.2)	50.95 (1.76)	0.03
L thigh	65.51 (2.60)	60.73 (1.4)	0.10
SHIM score	24.27 (0.33)	2.9 (0.20)	0.0001

Table 4. Penile and thigh StO<sub>2</sub> in men in older and younger men

	Age < 60 n = 94	Age > 60 N = 77	
Age	50.36 (0.77)	68.79 (0.87)	0.001
R thigh	60.10 (1.17)	57.35 (1.32)	0.12
R corpora	48.36 (1.89)	41.71 (2.14)	0.02
Glans	73.07 (0.95)	72.80 (1.087)	0.85
L corpora	54.58 (1.7)	48.21 (2.02)	0.04
L thigh	53.58 (1.79)	48.21 (2.02)	0.164
SHIM score	13.5 (0.92)	5.29 (1.0)	0.001

a 98% correlation to blood gas data in vitro and in vivo. In this group, study measurements were collected instantaneously without pain or distress to the patient.

There was a tremendous improvement in the StO<sub>2</sub> of the corpora and the glans with administration of intraurethral or injectable PGE<sub>1</sub>. As expected, the impotent group was older, had more endothelial risk factors, and included a larger proportion of individuals post-RRP. The StO<sub>2</sub> in the flaccid state of the men with ED differed significantly from the non-ED patients. Of the group of ED patients, approximately 50% were postprostatectomy. There was no significant difference in StO<sub>2</sub> of men with ED after RRP vs non-RRP, despite a marginally significant difference in age (61 vs 56 years, *P* < .04) and a significant difference in SHIM score (3 vs 13, *P* < .001). Despite the etiology, there appears to be a chronic state of penile hypoxia seen with severe ED and with advancing age. This chronic hypoxia leads to less NPT with eventual corporal fibrosis and progressive and irreversible ED.

The hemoglobin dissociation curve is useful in understanding penile StO<sub>2</sub> measurement. This curve relates

StO<sub>2</sub> and pO<sub>2</sub> in the blood and tissues. The relationship between StO<sub>2</sub> and the tissue pO<sub>2</sub> is dependent on many factors, but like the hemoglobin dissociation curve is nonlinear. The affinity of hemoglobin (Hb) for oxygen increases as successive molecules of oxygen bind until saturation, at which point the curve plateaus (60 mm Hg). Below 60 mm Hg, small fluctuations in pO<sub>2</sub> lead to a significant drop in StO<sub>2</sub> and significant hypoxia. P<sub>50</sub> is a conventional measure of affinity for oxygen, indicating the pO<sub>2</sub> at which Hb is 50% saturated (26.83 mm Hg). In our ED population the flaccid corporal saturation averaged less than 50%. With the loss of NPT, particularly after RRP, the corpora are chronically a profoundly hypoxic microenvironment. The difference between the corporal and glanular saturation probably reflects the different blood supply. Though the thinness of the glanular epithelial layer might be implicated as a reason for increased StO<sub>2</sub>, the thigh with its much thicker dermis and subcutaneous layer consistently had a higher StO<sub>2</sub> than the flaccid corpora.

Application of PGE<sub>1</sub> to this group resulted in near arterialization of the corpora. PGE<sub>1</sub> raised the StO<sub>2</sub> 150 percent to 76.58%, which corresponds to a pO<sub>2</sub> of 41.8 mm Hg. The increase in corporal StO<sub>2</sub> with PGE-1 supports the studies of Montorsi showing the value of postoperative PGE-1 injections in the recovery of erectile function after RRP.

This study serves to provide data on flaccid and erect StO<sub>2</sub> levels in men with and without ED. We demonstrate the use of a novel, noninvasive, accurate method of measuring intracavernosal oxygenation both in the flaccid and erect state.

### Conclusions

There exists a significant difference in the glanular and corporal StO<sub>2</sub> in the flaccid and erect states. Men with ED demonstrate significantly lower flaccid corporal StO<sub>2</sub> than men without ED. Administration of penile vasoactive materials results in arterialization of corporal and glanular blood. The Odyssey is a noninvasive diagnostic tool which is useful for measurement of penile oxygenation in patients. Future prospective data collection is needed to correlate penile StO<sub>2</sub> in specific

Table 5. StO<sub>2</sub> measurements in the flaccid and erect states for non-ED and ED patients

Site	StO <sub>2</sub> mean (%) (All)	Pre-PGE-1 StO <sub>2</sub> Mean (%)	Post-PGE-1 StO <sub>2</sub> Mean (%)	Mean StO <sub>2</sub> % Change	<i>P</i> Value
Right thigh	59.34 (11.29)	59.09 (10.01)	56.83 (10.7)	-1.50	> .13
Right corpora	49.14 (18.31)	45.23 (17)	76.58 (16.14)	150	< .001
Mid-glans	72.63 (9.7)	72.34 (9.22)	89.80 (9.25)	26	< .001
Left corpora	51.50 (17.17)	52.50 (16.08)	80.42 (12.46)	105	< .001
Left thigh	62.20 (12.25)	62.20 (10.73)	64.06 (11.73)	9	> .31

populations, such as diabetics and hypogonadal and RRP patients. This technique of tissue oximetry may to help further elucidate the relationship between corporal hypoxia and the development and progression of ED and possibly its treatment and prevention.

## References

- Choi S, Min K, Kim NN, Munarriz R, Goldstein I, Traish AM. Laser oximetry: a novel noninvasive method to determine changes in penile hemodynamics in an anesthetized rabbit model. *J Androl.* 2002;23:278–283.
- Fraiman MC, Lepor H, McCullough AR. Changes in penile morphometrics in men with erectile dysfunction after nerve-sparing radical retropubic prostatectomy. *Mol Urol.* 1999;3:109–115.
- Karacan I, Salis PJ, Hirshkowitz M, Borreson RE, Narter E, Williams RL. Erectile dysfunction in hypertensive men: sleep-related erections, penile blood flow and musculovascular events. *J Urol.* 1989;142:56–61.
- Karacan I, Salis PJ, Ware JC, Dervent B, Williams RL, Scott FB, Attia SL, Beutler LE. Nocturnal penile tumescence and diagnosis in diabetic impotence. *Am J Psychiatry.* 1978;135:191–197.
- Kim N, Vardi Y, Padma-Nathan H, Daley J, Goldstein I, Saenz de Tejada I. Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. *J Clin Invest.* 1993;91:437–442.
- Kim NN, Kim JJ, Hypolite J, Garcia-Diaz JF, Broderick GA, Tornheim K, Daley JT, Levin R, Saenz de Tejada I. Altered contractility of rabbit penile corpus cavernosum smooth muscle by hypoxia. *J Urol.* 1996;155:772–778.
- Klein LT, Miller MI, Buttyan R, Raffo AJ, Burchard M, Devris G, Cao YC, Olsson C, Shabsigh R. Apoptosis in the rat penis after penile denervation. *J Urol.* 1997;158:626–630.
- McCullough AR. Prevention and management of erectile dysfunction following radical prostatectomy. *Urol Clin North Am.* 2001;28:613–627.
- Padma-Nathan H, McCullough A, Forest C. Erectile dysfunction secondary to nerve-sparing radical retropubic prostatectomy: comparative phosphodiesterase-5 inhibitor efficacy for therapy and novel prevention strategies. *Curr Urol Rep.* 2004;5:467–471.
- Schwartz EJ, Wong P, Graydon RJ. Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. *J Urol.* 2004;171:771–774.
- Tamura M, Kawanishi Y, Furukawa A, Numata A, Yusa M, Imagawa A. [Ligation of the crura penis: surgical treatment for venous impotence]. *Hinyokika Kyo.* 1990;36:127–130.
- User HM, Hairston JH, Zelner DJ, McKenna KE, McVary KT. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. *J Urol.* 2003;169:1175–1179.
- Xu X, Zhu W, Padival V, Xia M, Cheng X, Bush R, Christenson L, Chan T, Doherty T, Latridis A. Validation of NIRS in measuring tissue hemoglobin concentration and oxygen saturation on ex vivo and isolated limb models. *Proc SPIE.* 2003;4955:369.