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Changes in Penile Morphometrics in Men with Erectile Dysfunction after Nerve-Sparing Radical Retropubic Prostatectomy

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ABSTRACT

There have been anecdotal reports of a decrease in penile size in men with erectile dysfunction (ED) after nerve-sparing radical retropubic prostatectomy (NSRRP). Penile circumference and length measurements are obtained by one physician from 100 men, age 47 to 74, who presented at various intervals (1.7–27.6 months) for the treatment of ED after NSRRP from 1994 through 1997. All patients were asked to complete a brief male sexual function inventory at their initial visit. Penile measurements were obtained both in the flaccid and erect states, with erections being induced with intracorporal injections of Trimix. The sexual inventory scores were compared with those of an age-matched control cohort of 130 men presenting for evaluation of ED during the same time period and 132 age-matched men who completed the inventory at the time of a prostate screening. By self-report, men experiencing ED after NSRRP had better libido but more severe ED than men presenting with ED of other causes. There was a decrease in all penile dimensions after NSRRP. The flaccid and erect measurements of length and circumference decreased 8% and 9%, respectively after surgery ($p < 0.05$). The most substantial change occurred between the first 4 and 8 months postoperatively. The average change in volume between the first 4 and 8 months was 19% to 22% in the flaccid and erect state, respectively. There is a significant decrease in penile size in men with ED after NSRRP. The etiology may be denervation smooth muscle atrophy, apoptosis, or hypoxia-induced damage to the corpora. Further research is needed to elucidate the nature of these postoperative changes.

INTRODUCTION

ERECTILE DYSFUNCTION (SD) is common after a radical prostatectomy. Nerve-sparing techniques are well established and can provide potency rates of approximately 60% to 70%,[1] although the return of function may take as long as 18 months. Many patients who have presented postoperatively for the evaluation of ED have reported a decrease in penile size. Although this change is frequently reported, there have been no studies in the literature documenting that there is actually any change in penile size after radical prostatectomy.

Reports of decreased penis size have prompted investigations into the etiology of such changes. A study by Klein et al.[2] in an animal model was performed in an attempt to determine a possible explanation for a decrease in penile dimensions after denervation. Those investigators concluded that after denervation of the rat penis, apoptosis of the erectile tissue occurred, The apoptosis could explain the changes in penis size after radical prostatectomy. No study has been performed to analyze the changes in penile morphometrics in the human after NSRRP. We retrospectively analyzed penile morphometric data obtained at the time of penile Doppler ultrasonography to determine possible changes in penile dimensions after NSRRP.

PATIENTS AND METHODS

One hundred men aged 60.6 ± 0.7 (range 47–74 years) who underwent bilateral NSRRP by a single surgeon (HL) between 1995 and 1997 presented at different intervals postoperatively for evaluation of ED. All men were potent by history prior to surgery. None of the patients had received adjuvant or neoad-

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TABLE 1. CHARACTERISTICS OF NSRRP AND NONSURGICAL GROUPS (PERCENT OF PATIENTS)

	NS (n = 130)	*NSRRP (n = 100)*	p *Value*
Smoking history	16.1	16.5	NS
Diabetes	17	4	<0.05
Hypertension	43.3	30	NS
Alcohol abuse	16	4	<0.05

juvant radiation or hormonal therapy. A control group of 130 age-matched men 47 to 74 (mean 60.7 ± 0.4) years who presented with ED without a history of pelvic surgery (NS group) were included for comparison.

All patients completed a validated questionnaire[3] at the time of their presentation. The questionnaire included items on sexual drive, erection quality, ejaculation quality, problem assessment, and overall satisfaction. For comparison purposes, the sexual function inventory from an age-matched cohort of 132 men presenting during the same time period for a prostate cancer screening was used.

Alcohol use, tobacco use, a history of diabetes mellitus, and hypertension were documented.

Penile morphometrics were obtained from all of the patients by a single observer (AM) at the time of penile color duplex ultrasound scanning. The penis length and circumference were initially measured from symphysis to penile tip in the flaccid state in the recumbent position. A second measurement at the time of maximum erection was performed following intracorporal injection of 0.3 mL of Trimix (20 μg of PGE-1, 30 mg of papaverine, and 1 mg of phentolamine per milliliter). The injection was uniformly administered laterally into the left corpus cavernosum with a 29-gauge needle. Patients who had not responded maximally by 10 min were asked to stand for 2 min to enhance the quality of their erections. The increased venous congestion in the standing position always resulted in an improved erection. A qualitative assessment of penile tumescence was made by both the attending urologist and the patient.

Changes in penile volume were calculated based on the formula volume = $\pi r^2 \times h$ and assumed that the penis is shaped like a cylinder with the height equal to the length from symphysis to the penile tip and the radius equal to the penile circumference/2π.

Linear regression evaluations were done on the entire group, and categorical analysis was performed on patients grouped by time interval from surgery (A=0–4 months, B=4–8 months, C=8–12 months, D > 12 months postoperatively).

The data were analyzed via the SAS statistical software program. ANOVA and the *t*-test were used. Variances are reported as the standard error of the mean.

RESULTS

The average time from NSRRP was 9.4 (0.5) months. No patient had erections sufficient for vaginal penetration. Eighty-three percent of the patients had cancers of stage pT2 or less. An age-matched cohort of 130 men presenting for ED evaluation during the same time period was used for comparison. Evaluation of risk factors for ED; i.e., smoking history, hypertension, diabetes, and alcohol abuse, revealed significant differences only in the incidence of diabetes and alcohol abuse. The NSRRP group overall had fewer comorbidities (Table 1).

A validated male sexual function survey revealed significant decreases in all fields questioned except sexual drive in the NSRRP *v* the NS group (Table 2). The NSRRP group demonstrated significantly greater sexual drive but the same level of overall dissatisfaction. Both groups showed significant decreases in all fields except sexual drive from an age-matched population of 132 men presenting at a prostate cancer screening. The sexual drive of the NSRRP group was equal to that of the cancer screening group.

As determined by the patient and the observer (AM), the percentage of patients manifesting an erection satisfactory for penetration during the penile duplex Doppler examination was identical in the two groups (75%). The erections were not improved by redosing with Trimix.

The average penile dimensions were similar in the NSRRP and NS groups except for the flaccid circumference, which was lower in the NSRRP group ($p < 0.05$) (Table 3).

When the NSRRP group was analyzed as a function of time since surgery, we demonstrated a negative correlation between time and penile morphometrics. The erect and flaccid dimensions decreased with time after surgery; erect circumference ($r = 0.23$; $p < 0.05$), erect length ($r = 0.31$; $p < 0.05$), flaccid circumference ($r = 0.28$; $p < 0.05$), and flaccid length ($r = 0.25$; $p < 0.05$) (Fig. 1).

On the basis of the changes in the length and circumference the calculated maximum changes in volume were 19% in the flaccid state and 22% in the erect state.

The patients were then grouped in time intervals to determine if a period could be identified during which the morpho-

TABLE 2. COMPARISON OF MEAN MALE SEXUAL FUNCTION INVENTORY (SEM) IN AGE-MATCHED PROSTATE SCREENING GROUP, NS GROUP, AND NSRRP GROUP

Sexual Function Field (Maximum Score)	*Prostate Screen (n = 132)*	*NSRRP (n = 100)*	*NS (n = 130)*
Sexual drive (8)	4.46 (0.19)	4.3 (0.2)	3.6 (0.2)
Erection quality (12)	7.9 (0.28)	1.45 (0.25)	2.9 (0.23)
Ejaculation quality (8)	6.3 (0.23)	2.23 (0.26)	3.7 (0.23)
Problem assmt (12)	9.1 (0.29)	3.27 (0.32)	3.39 (0.29)
Satisfaction (4)	2.5 (0.1)	0.77 (0.11)	0.75 (0.1)
Total score (44)	30.3 (0.87)	11.9 (0.96)	14.5 (0.86)

TABLE 3. PENILE MORPHOMETRICS (SEM) BY GROUP

	Flaccid Length (mm)	*Erect Length (mm)*	*Flaccid Circ. (mm)*	*Erect Circ. (mm)*
Group A (0–8 mos)	125 (6)	168 (5)	90 (3)	121 (3)
Group B (4–8 mos)	114 (2)	153 (3)	84 (1)	119 (2)
Group C (8–12 mos)	120 (4)	149 (5)	85 (2)	115 (3)
Group D (12–16 mos)	116 (4)	152 (5)	83 (2)	116 (2)
Avg NSRRP	118 (2)	154 (2)	85 (1)	118 (1)
Avg NS	121 (2)	152 (1)	87 (1)	116 (1)

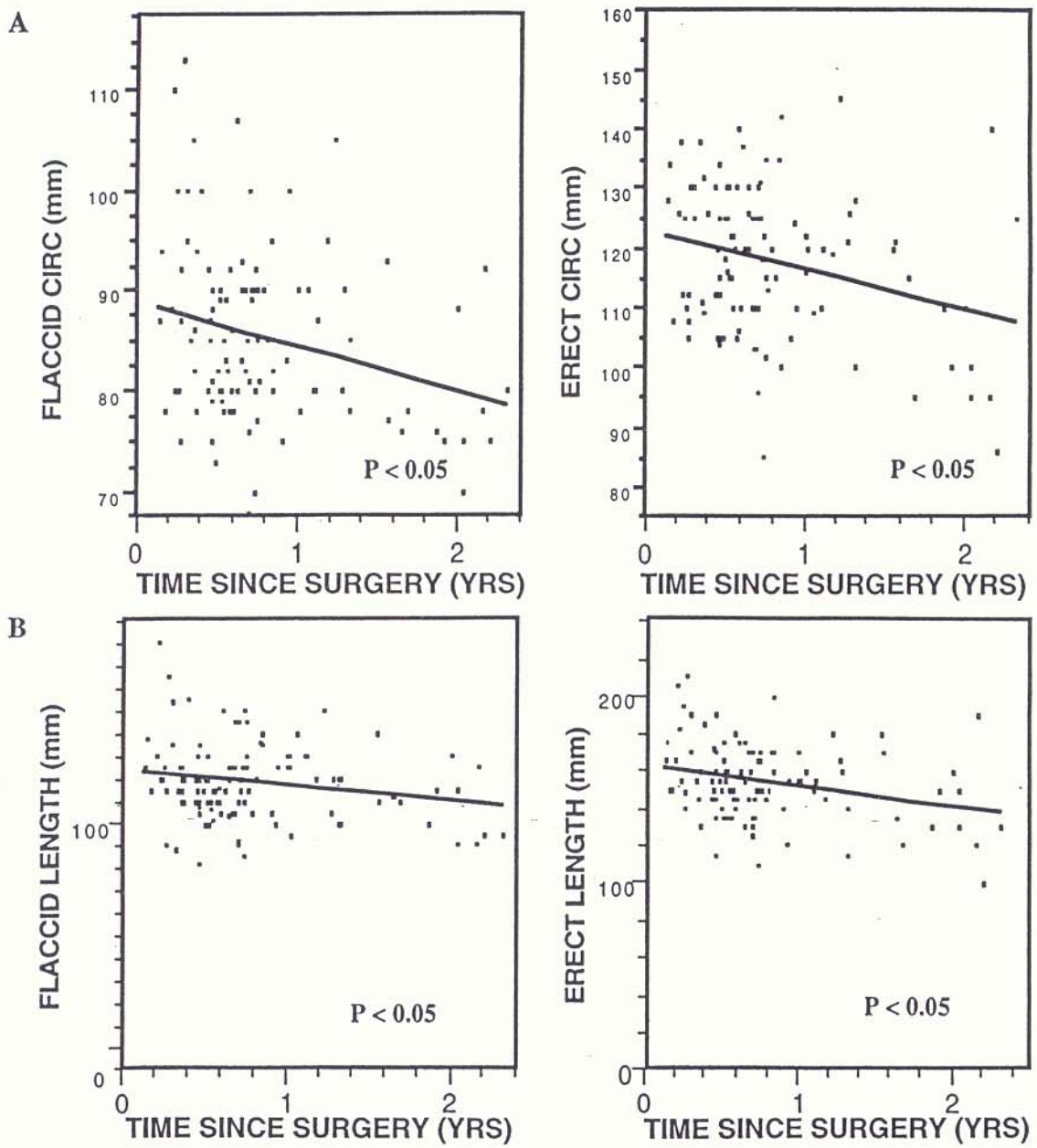

FIG. 1. Changes in penile circumference (A) and length (B) after surgery.

metric changes took place. The NSRRP group was categorized into four groups: 0 to 4 months (A group: 17 patients), 5 to 8 months (B group: 38 patients), 9 to 12 months (C group: 21 patients), and >12 months (D group: 24 patients) postoperatively. The average age differed significantly among the groups: A = 54 years, B = 58.9; C = 62.1; D = 63.1 ($p < 0.05$). However, none of the dimensions measured differed significantly with age.

The patients showed a decrease in all penile dimensions as the time interval from surgery increased. The decrease began early, as the greatest change in dimensions was demonstrated between the A and B groups. The changes occurred, for the most part, within the first 6 months (Fig. 2).

DISCUSSION

This study represents the only report in the literature of penile morphometrics after NSRRP. All surgery was performed by a single surgeon, thus minimizing differences in surgical

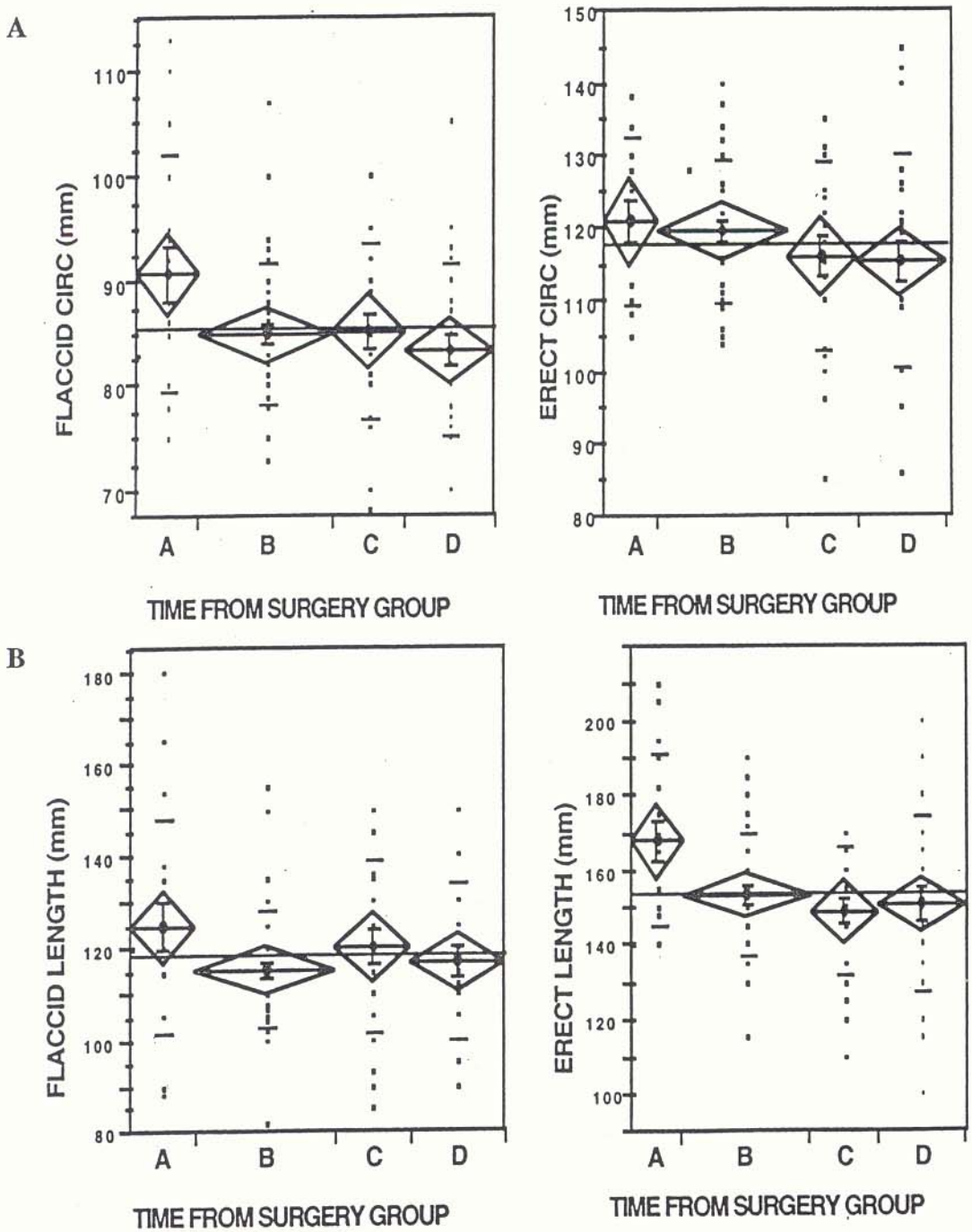

FIG. 2. Changes in penile circumference (A) and length (B) according to time since prostatectomy.

technique as a cause of the findings. Bilateral nerve-sparing prostatectomy was performed in 90% of the patients included in this study group.

The extent of the sexual dysfunction in the NSRRP group was well documented by the sexual function questionnaire (see Table 2). Of interest is that the NSRRP group did not demonstrate a decrease in sexual desire in comparison with an age-matched prostate screening group, despite their relatively recent cancer diagnosis and surgery. The sex drive was better ($p < 0.05$) in the NSRRP group than in the NS cohort. The short duration of their ED compared with that in NS patients may account for the difference in libido.

We found that the NSRRP group had average penile morphometrics similar to those in an age-matched group of similar men presenting for ED who did not have a surgical history. That there was so little difference in dimensions is not surprising. The findings that the average dimensions after NSRRP are no different than those of other men with ED could be explained by hypothesizing that the NS men already have end-organ (penile) changes from their longstanding ED. Historically, the average man waits 5 years before seeking help for his ED. The average NSRRP patient had experienced ED for an average of only 9 months in our study. Within these 9 months, our study group likely experienced end-organ changes associated with ED, leading to a decrease in penile size similar to that in the NS patients.

Because the etiology of postprostatectomy ED is incompletely understood, the explanation of our findings of a decrease in penile morphometrics can only be hypothetical. The injuries that lead to ED are likely intimately related to a decrease in penile size after surgery. Theories have evolved regarding the etiology of postprostatectomy impotency and involve primarily nerve and vascular damage.

Prior to the development of the nerve-sparing prostatectomy, ED was attributed primarily to intraoperative nerve injury. Through the work of Walsh and Lepor and their associates, the neurovascular bundles have been described, and preservation techniques have been developed.[4,5] However, even though the nerve-sparing technique is utilized, potency rates after surgery vary tremendously, with reported rates between 11% and 70%.[1, 6–8]

Because of persistent ED despite preservation of the nerves, vascular injuries have been implicated as a cause for the ED. Damage to the accessory branches of the pudendal artery has been hypothesized as the mechanism.[9] These branches have been reported in 70% of cases, with their termination as cavernosal arteries in 75%.[9] Because of these findings, careful attention has been given to preserving these arteries, with no improvement in potency rates.[10] In addition, Padma-Nathan and Goldstein have suggested that the pathophysiology of ED after RRP is venous leak from the corpora.[11]

Despite the fact that the exact contribution of vascular and neuronal injury to ED after prostatectomy is unknown, it is reasonable to assume that these insults might, in time, explain the changes that we demonstrated in penile size. We can only theorize at this time as to the cause of this atrophy. Some possibilities are nerve injury leading to denervation atrophy, apoptosis, or sympathetic/parasympathetic imbalance and vascular injury leading to hypoxia with subsequent fibrosis.

Denervation of the corpora may be responsible for shrinkage of the tissue (denervation atrophy). This principle is not new, as others have demonstrated atrophy of muscle groups in the absence of vascular injury following nerve injury. Kirchner[12] described atrophy of the muscles innervated by the left laryngeal nerve after resection of this nerve in an animal model. Severe atrophy occurred in the absence of local vascular injury. Zealer et al.[13] studied the cricoarytenoid muscle after denervation and found fibrosis 3 to 7 months after the injury. Our findings are similar, as we found the most notable decrease in size between 4 and 8 months. Atrophic changes thus may occur in the corporal smooth muscle after radical prostatectomy, with or without changes in vascular supply, secondary to denervation atrophy.

In addition, the smooth muscle cells of the corpora may be dependent on neuronal input for function and growth. The corporal cells may then be "incapacitated" without nerve stimulation or may even undergo apoptosis. These theories are also not new. Transcutaneous application of low-frequency electric current has been used to treat denervated striated muscle and is applied to prevent or treat muscular atrophy. On the basis of this premise, Stief and associates[14] utilized electromyostimulation of the corpus cavernosum smooth muscles and improved erectile dysfunction in 37% of patients with ED. How this stimulation provides impotent patients with increased function is unknown. This stimulation, which leads to increased activity, might also prevent corporal atrophy and prevent a decrease in penile size after prostatectomy.

The nonadrenergic noncholinergic nervous system has been determined to be the principal pathway of corporal smooth muscle relaxation, the main neurotransmitter being NO. Nitric oxide induces intracavernous smooth muscle relaxation leading to erectile activity.[15,16] Carrier et al.[17] demonstrated a significant decrease in NO-producing nerve fibers after cavernosal nerve transection in an animal model. The adrenergic nerves are not affected by cavernosal nerve transection. With intact adrenergic nerves, there may be a significant imbalance in the regulatory input of the cavernosal tone following injury to the cavernosal nerves. The loss of the relaxation response normally induced by NO may increase the overall tone of the corporal smooth muscle, resulting in an overall decrease in penile size.

Recently, Klein et al.[2] studied rat corpora to see if denervation increased the rate of apoptosis. This study was based on the premise that the nerves to the penis produce some factor(s) that serve a protective role for penile tissue. The investigators postulated that severing the cavernous nerves would result in tissue loss through programmed cell death (apoptosis). They found by DNA extraction studies and by Northern blot analysis for protein markers of cell death that apoptosis followed transection of the cavernous nerves. In addition, there was evidence of apoptotic nuclei on examination of the cavernous tissue.[2] Could similar changes be occurring in the human corpora after radical prostatectomy, causing both impotence and decreased penile dimensions? Further work is needed to investigate whether apoptosis occurs in human corpora after denervation.

Hypoxia of the corpora may induce changes leading to a decrease in penile size. Hypoxia has been shown to alter cytokine and prostaglandin production in tissues, leading to fibrosis. This fibrosis may explain the observed changes in penile morphometrics.

Whether the ED is secondary to vascular or nerve injury, men who have ED after prostatectomy do not have normal nocturnal oxygenation of their corpora. The corpus cavernosum is exposed to different oxygen tensions depending on the erectile state of the penis, as the pO_2 ranges from 2 to 40 mm Hg in the flaccid state to 80 to 100 mm Hg in the erect state.[18] Men normally have three to five erectile episodes each night, with each one typically lasting from 20 to 40 min.[19] This accounts for 1 to 3.5 h of exposure of the corpora to high arterial oxygen tension. After radical prostatectomy, these erections are virtually absent in men with ED (unpublished data).

Hypoxia induces the expression of transforming growth factor-beta (TGF-β) (associated with fibrosis) in dermal fibroblasts[20] and aortic smooth muscles.[21] Similarly, hypoxia increases TGFβ and endothelin in the penis, leading to vasoconstriction, corporal fibrosis, and a subsequent decrease in erectile function.[22–24] It has been suggested that injections of PGE_1 suppress TGFβ_1-induced collagen formation (through oxygenation) in human corpus cavernosum smooth muscle cells and may prevent new fibrotic lesions associated with impotence.[25] Montorsi and coworkers[26] found that early (1-month) postoperative administration of alprostadil injections significantly increased the recovery rate of spontaneous erections after nerve-sparing prostatectomy. Those workers believe that the increased activity was attributable to greater oxygenation of the corpora, limiting the development of hypoxia-induced tissue damage. It may be found that the same treatment would prevent decreases in penis size in postprostatectomy patients through changes in cytokine and prostaglandin synthesis. As the morphometric changes that we observed occurred in the first 4 to 8 months, an argument for aggressive early injection treatment could be made.

The difference in age that exists between the different groups might be argued to be a contributory factor in the morphometric changes. The increasing age with increasing interval indicates that, in our population, older men tend to present for the evaluation of ED at a greater interval after surgery. Banya et al[27] described age-related changes of the smooth muscle and collagen fibers in human cadavers with unknown prior potency status. They found a decrease in smooth muscle with age by histologic evaluation. In our NSRRP and NS groups; none of the morphometric measured differed significantly with age, thus discounting age as an issue.

The argument that penile shortening might be related to the surgical removal of a segment of urethra is contradicted by the observation that penile circumference also decreased and that the earlier postoperative measurements were greater than later measurements.

CONCLUSION

The exact mechanism of injury to the penile structures causing ED after NSRRP is unknown. We have demonstrated that there is a decrease in penile size after prostatectomy in a population with ED and assume that the morphometric changes are related to an intraoperative injury. The pathophysiology is most likely multifactorial, related to the neurovascular issues discussed above. The NSRRP patient with ED presents a unique model, in that the exact time of onset of ED is known. It remains to be seen whether early treatment can prevent some of the atrophic changes and expedite recovery of erectile function. Prospective studies are needed into the mechanism of the dysfunction and functional changes that occur in the penis after radical prostatectomy.

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