

# Is sildenafil failure in men after radical retropubic prostatectomy (RRP) due to arterial disease? Penile duplex Doppler findings in 174 men after RRP

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**Sildenafil is frequently the first-line treatment for post-radical retropubic prostatectomy (RRP) erectile dysfunction (ED) with maximum treatment satisfaction rates of 43%–80%. The etiology of erectile dysfunction after RRP has been attributed to psychogenic, vascular, veno-occlusive or nerve injury causes. The purpose of this study was to gain insight into the penile duplex Doppler arterial parameters in men with ED after RRP who failed sildenafil. The purpose was to assess whether sildenafil failure after RRP is associated with underlying corporal arterial disease. A total of 174 consecutive men presenting with sildenafil refractory ED after nerve-sparing RRP underwent color duplex penile Doppler evaluation with vasoactive injection. Mean age was 59.6 y and mean time from surgery was 11.6 months. Some 81% (141/174) of the men had no pre-operative ED (PED). Significant differences in penile duplex Doppler parameters for arterial disease were seen between men with and without PED. In men without PED, 19% (27/141) manifested arterial insufficiency. However, in men with PED, 50% (16/33) demonstrated arterial disease. Nerve sparing status did not affect the presence of arterial disease. Sildenafil refractory erectile dysfunction after RRP in men without PED is not predominantly associated with penile Doppler parameters consistent with arterial insufficiency.**

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## Introduction

The incidence of erectile dysfunction (ED) following radical retropubic prostatectomy (RRP) ranges from 10 to 100%,<sup>1–8</sup> depending on the age of the patient, length of time from surgery, stage of the disease, co-existing morbidities, pre-operative sexual function, the nerve-sparing nature of the surgery, and the experience of the surgeon. Sildenafil has become the first-line treatment for post-RRP ED because of its safety and ease of administration. Maximum treatment satisfaction rates of 43–80% have been reported.<sup>9,10</sup> The etiology of ED after RRP has been attributed to psychogenic, vascular,<sup>11–14</sup> veno-occlusive,<sup>15,16</sup> nerve injury<sup>17</sup> factors, or a combination of all four. Sanchez-Ortiz has described a 50% incidence of arterial disease in non-RRP men who failed sildenafil.<sup>18</sup> The purpose of this study is to see

whether sildenafil refractory erectile dysfunction after RRP may be associated with underlying arterial disease.

## Materials and methods

A total of 174 consecutive men presenting with ED after nerve-sparing RRP between 1994 and 2000 underwent color duplex penile Doppler with vasoactive injection. As part of our post-RRP ED evaluation, we routinely perform penile duplex Doppler evaluations prior to initiating injection treatment for their ED. The duplex Doppler allows us to better determine and understand the underlying penile vascular pathology and establish an optimal starting dose of trimix, minimizing the risk of priapism. All men in our study were sildenafil failures. Sildenafil failure was defined by the inability to achieve an adequate erection for sexual function after taking 100 mg of sildenafil on at least six occasions. Criteria for RRP included a clinically organ-confined adenocarcinoma and a life expectancy of at least 10 y. No patients underwent adjuvant external beam radiation or hormonal

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therapy, post-operatively. Nerve-sparing status was derived from the operative notes. Pre-operative erectile function was assessed by pre-surgical history documented by the surgeon.

Ultrasounds were performed with an ACUSON Aspen Advanced system after trimix injection (6 µg PGE-1, 18 mg papaverine, and 0.3 mg phentolamine). The ultrasonographer was blinded as to the nerve-sparing status. Doppler measurements were performed in the recumbent position from the ventral aspect of the penis. Scanning angle was 60°. All injections were performed in the left corpora. Penile doppler parameters measured included: (1) pre-injection—cavernous artery diameters (CAD) and peak systolic velocities (PSV) of the cavernous artery (CA); and (2) post injection—CAD, systolic rise times (SRT) and PSV of the CA. SRT was defined by the time from the start of systole to PSV.

We used three different criteria for arterial insufficiency. Arterial insufficiency was defined as percentage change in CAD < 50%, SRT > 0.1 s, or PSV < 25 cm/s.

Anova/*t*-test and linear regression were performed using the JMP statistical software program version 3.2.2 developed by the SAS Institute. All statistically significant changes represent differences with *P* < 0.05 using the paired *t*-test.

## Results

### Results in overall group

The mean age was 59.6 ± 6.8 y and mean time from surgery was 11.6 ± 9.7 months. In all, 81% (141/174) of men did not have pre-operative erectile dysfunction (PED). A total of 85.6% underwent bilateral nerve sparing prostatectomy (BNSRRP); 90% of the men with PED had BNSRRP. Pathology stage distribution was 77.3, 21.2 and 1.5% for pT2, pT3 and pT4, respectively.

Since no significant difference was seen in the parameters between corporal sides, the results are reported as the average of both sides. Significant

**Table 1** Comparisons of Doppler parameters in men with and without pre-operative erectile dysfunction

	NO ED (s.d.), n = 141	ED (s.d.), n = 33	P-value
Age (y)	59 (7.1)	62 (5.4)	0.025
Pre-injection CA CAD (mm)	0.60 (0.30)	0.61 (0.03)	0.76
Pre-injection PSV (cm/s)	11.39 (3.87)	10.52 (3.36)	0.25
Post-injection CA CAD	1.13 (0.19)	1.95 (0.20)	0.05
Post-vs pre-CAD ratio	1.84 (0.48)	1.64 (0.50)	0.07
Post-CA SRT	0.09 (0.02)	0.11 (0.03)	0.0003
Post-PSV	57.27 (19.25)	45.54 (20.35)	0.003

differences were seen between men with and without PED. The group with PED was slightly older and demonstrated more arterial disease (Table 1).

### Arterial disease in men without PED (141/174)

We looked for evidence of arterial disease or injury in 141 men without PED. Because of the lack of accepted absolute standards of the Doppler parameters for arterial disease, three different parameters, PSV, SRT and percentage change in CAD, were evaluated. The most difficult measurement was the CAD because of the small caliber of the CA. Lue<sup>19</sup> described average 'normal' internal diameters of the CA as 0.51 and 0.89 mm before and after injection, respectively, which corresponds to a 75% change. Our average pre- and post-injection CAD exceeded those values (Table 2 and 3). Percentage change in CAD was 50% or less in 4.9% (7/141), between 50 and 75% in 22% (31/141), and greater than 75% in 73% (103/141). Severe arterial disease by PSV (PSV < 25 cm/s) was seen in 2.1% (3/141), equivocal disease (PSV = 25–35 cm/s) in 10% (14/141), and no arterial disease (PSV > 35 cm/s) in 88.6% (125/141). An SRT of > 0.1 s has been shown to be associated with arterial disease.<sup>20</sup> SRTs were normal (< 0.1 s) in 83% (117/141). SRT appeared to be the most sensitive parameter, followed by CAD and PSV, with 17, 5 and 2%, respectively, demonstrating abnormal values. PSV correlated strongly with SRT (*r* = - 0.463). Percentage change in CAD correlated poorly with SRT and PSV (*r* = of - 0.10 and 0.23).

Of 141 men without PED, 19.1% (27/141) met at least one criterion for arterial disease, 5% (7/141) met two, and none met three criteria.

However, in the 33 men with varying degrees of PED, 48% (16/33) demonstrated at least one abnor-

**Table 2** Pre-injection parameters in all patients (n = 174)

Pre-injection	Right corpora (s.d.)	Left corpora (s.d.)
Corporal diameter (mm)	8.5 (1.4)	8.4 (1.4)
CAD (mm)	0.57 (0.14)	0.57 (0.14)
PSV (cm/s)	11.3 (3.9)	11.3 (3.9)

**Table 3** Summary of post-injection Doppler parameters in all patients (n = 174)

Post-injection	Right corpora (s.d.)	Left corpora (s.d.)
CAD (mm)	1.1 (0.19)	1.1 (0.19)
CA SRT (s)	0.0913 (0.023)	0.0913 (0.026)
CA Flow (cm <sup>3</sup> /s)	9.04 (5.3)	9.97 (6.4)
CA PSV (cm/s)	55.56 (22.2)	54.31 (20.4)

mal arterial parameter, 21% (7/33) demonstrated two, and 3% (1/33) demonstrated all three.

### *Nerve sparing status and arterial disease*

Nerve sparing (NS) status did not appear to affect the presence of arterial disease. In a subset of 96 men without PED, we examined the effect of nerve sparing on the spared vs non-spared side. Average age was 59 y. Mean time from surgery was 13 months in the bilateral NS group and 8 months in the unilateral NS group. Using the three different criteria for arterial disease, there was no evidence of isolated arterial injury on the non-spared side.

## Discussion

This study represents the largest and most comprehensive penile duplex Doppler series in men after RRP and the only Doppler study in sildenafil refractory men after radical prostatectomy. By having a single surgeon and ultrasonographer, the variation in surgical and ultrasound scanning techniques are minimized. All men had failed sildenafil therapy. The low incidence PED in our study population is a reflection of the motivation of men seeking treatment at our center. Most men presented to our surgeon in order to maximize preservation of their erectile function.

Prior to the work of Walsh and Donker,<sup>21</sup> describing the neurovascular bundles, the majority of men undergoing RRP were impotent post-operatively. With the development of the nerve-sparing RRP, the incidence of post-operative erectile dysfunction decreased. Sildenafil allowed many men with borderline erectile post-operative function to regain their function. Yet a large percentage of men fail sildenafil.

Arterial insufficiency<sup>12</sup> and corporeal veno-occlusive dysfunction<sup>22</sup> have been implicated in ED after nerve-sparing RRP. While some authors reported that the arterial insufficiency might be due to an injury to the accessory pudendal artery, Blander<sup>22</sup> and Polascik<sup>23</sup> questioned the importance of the accessory pudendal artery. The accuracy of penile Doppler in the determination of arterial disease has been established.<sup>24,25</sup> Arterial disease appears to be a major factor in non-RRP men failing sildenafil.<sup>18</sup> We therefore questioned whether this might be the case after RRP.

We chose three methods of defining arterial insufficiency because of the lack of consensus in the literature as to the best way of defining arterial insufficiency. We wanted to maximize the sensitivity of detecting arterial disease. In our study, the incidence of arterial disease was low. Only 19% of

men without PED met one of the defined arterial disease parameters. No patients had all three, suggesting that none of our patients had severe penile arterial insufficiency. Men who had PED demonstrated 2.5 times (48 vs 19%) more arterial disease. As in previous studies, we found the percentage change in CAD to be the least reliable parameter of arterial disease, because of the difficulty in measuring the small arterial CA diameters accurately and reproducibly.<sup>24</sup>

A caveat of this study is the lack of control pre-operative Doppler measurements, measurements in a cohort of sildenafil-responsive men, and men with normal erectile function after RRP. It is possible that, although the prevalence of arterial disease in this population was low, it might have been even lower pre-operatively. The only way to definitively answer whether RRP affects the penile arteries is to have pre- and post-operative measurements. Although ideal, it is not practical to administer pre-operative Dopplers in this group of men.

Nonetheless, one would expect the men undergoing RRP to be in better physical condition than the general population, as they are selected for this treatment modality because they have a significant longevity and are 'surgical candidates'. The high degree of intact pre-operative erectile function in our population, that would be expected to have a greater than 50% prevalence of ED based on their age alone, suggests a healthier population. The inability to document significant arterial disease is therefore not surprising and also suggests that surgery itself does not have a negative impact on the penile arteries, as measured by penile Dopplers.

## Conclusions

The incidence of arterial insufficiency following nerve-sparing radical prostatectomy is low in a group of previously potent men presenting with sildenafil refractory erectile dysfunction.

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