Chapter 4
Pathophysiology of Nerve Injury and Its Effect on Return of Erectile Function

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Introduction

Dr. Patrick Walsh and his associates initiated the concept of attempting to preserve sexual potency following a radical prostatectomy (RP) when they originally described the anatomy of the cavernous nerves (CN) and the process of anatomical nerve-sparing radical prostatectomy [1, 2]. However, two decades passed until new surgical technology introduced the possibility of a near bloodless surgical field and dramatically improved visualization via laparoscopic and robotic radical prostatectomy popularized by Vallencien, Guilloneau, Abbou, and indeed many of the authors of this book. With these less invasive surgical approaches surgeons were better able to apply the principles of visual nerve preservation with retrograde and antegrade nerve-sparing approaches. However, anatomical preservation although critically important has and does not explain how or why potency recovery takes 2 years. The foundation of our modern understanding of nerve injury and healing originated with Sir Herbert Seddon in the 1940s who demonstrated the pathophysiology of injury and recovery in peripheral nerves [3]. Seddon's discoveries became the basis for many subsequent discoveries in the field of neuropathology and have also proven to be the basis upon which modern techniques of nerve preservation and reconstruction are based for various surgeries. Indeed, the application of Seddon's principles to the injury and recovery of function of the CN was only introduced in 2008. Clearly, basic neurosurgical concepts such as "dissecting the organ off of the nerve

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as opposed to dissecting the nerve off of the organ" originated from these seminal works. In as much as this has been a challenge, the major advances of magnified, 3D, high definition vision systems integrated with highly dexterous, robotic, microsurgical instrumentation have also provided many opportunities to advance our understanding of reducing "injury" to the CN while visualizing and preserving it. This chapter summarizes the basic anatomy and more importantly the pathophysiology of cavernous nerve injury and how our expanding knowledge of this topic will lead to future improvement of clinical outcomes.

Potency Outcomes Self-Assessment

The most critical component required for assessment and subsequent understanding of sexual outcomes following RP is obsessive collection and collation of validated self-reported baseline and follow-up questionnaires. The primary reason surgeons do not improve outcomes is the lack of personal experience and the uninformed assumption of "acceptable" results. It is imperative for the robotic surgeon to establish a surgical database of preoperative demographics and postoperative outcomes for critical self-evaluation. Self-assessment is a continual iterative process, and as the volume of ones cases increases, a personal database allows one to measure outcomes against published results. Through the process of self-assessment of outcomes, the surgeon can determine if there are specific troublesome technical or clinical issues. There are two important self-assessment tools: rigorous data collection and reviewing personal and "expert" video recordings.

The collection of data regarding patients' baseline demographics, intra and postoperative outcomes is essential. Preoperative data must be stringently collected as most functional outcomes are dependent on the baseline characteristics. A proposed minimum data collection design is a baseline International Index of Erectile Function (IIEF-5) also known as SHIM (Sex Health Index in Men), age, medical issues such as hypertension and diabetes, and testosterone levels (free and total). At baseline, Rosen et al. [4] demonstrated that an IIEF-5 score of 22–25 was highly predictive of normal erectile function. In our experience we have not seen a single case of recovery of sexual function following radical prostatectomy if the baseline IIEF-5 is below 15. Additionally, if a patient is dependent on a PDE inhibitor to achieve a given IIEF-5 score we recommend subtracting seven points to establish baseline function. Postoperative oncologic and continence data, in addition to complication rates, should be meticulously recorded to improve surgical technique and identify areas that may lead to improvements in patient outcomes.

Defining "recovery" of potency continues to be practically and theoretically a real challenge. Some authors arbitrarily define or recommend an IIEF-5 score of >16, 21, or 25 with or without PDEi; some attempt to simplify the matter by defining recovered potency as a patient reporting a score of 3 or higher for question 5 of the IIEF-5[4–7]. We suggest a quantitative and a qualitative assessment (Fig. 4.1). We define potency quantitatively (with or without PDE5 inhibitors) as an affirmative answer to 2 questions from EPIC questionnaire, (1) "Are your erections adequate

1. Do you presently have erections firm enough for penetration **Yes / No** Are they Satisfactory? **Yes / No**
2. Please circle the fullness you are able to achieve in your erections compared to before surgery?
3. **0% 10 % 25% 50% 75% 85% 90% 95% 100%**
4. Do you currently use any medications listed for potency? If Very Helpful-**VH**, if Slightly Helpful-**SH**, if Not Helpful-**NH**
   Viagra_____________ Levitra__________ Cialis__________ Muse__________ Other__________
   ______ None
5. If you have taken Viagra or Cialis, please describe: Daily Yes/No As Needed Yes/No

Date started ____________________ and **for how many weeks**__________

1. How do you rate your confidence that you could get and keep an erection?

Very low	Low	Moderate	High	**Very High**
1	2	3	4	5

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner).

No sexual activity	Almost never or never	A few times (less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	**Almost Always Or Always**
0	1	2	3	4	5

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Did not Attempt intercourse	Almost never or never	A few times (less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	**Almost Always Or Always**
0	1	2	3	4	5

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Did not attempt intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	**Not Difficult**
0	1	2	3	4	5

5. When you attempted sexual intercourse, how often was it satisfactory to you?

Did not attempt intercourse	Almost never or never	A few times (less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	**Almost Always Or Always**
0	1	2	3	4	5

SCORE__________

Fig. 4.1 IIEF-5 and quantitative and qualitative sexual function assessment used for pre and post-operative assessment of potency

for vaginal penetration?" and (2) "Are your erections satisfactory?"[8]. For qualitative assessment we recommend the IIEF-5. Additionally, we have found that simply asking the patient what percent of their baseline erectile function they have regained postoperatively can be most helpful, especially in the early months following surgery when erections are not adequate (Fig. 4.1 question 3).

Recording case videos can be extremely advantageous to not only the novice surgeon but those with experience as well. Reviewing ones procedure is particularly useful for difficult cases and for cases with excellent functional outcomes.

Gross Anatomic Studies of the Cavernous Nerves

The anatomic basis for erectile function [1] and the subsequent technique for nerve-sparing radical retropubic prostatectomy were initially described by Walsh and associates in 1983 [2]. The authors described the pathways of the parasympathetic

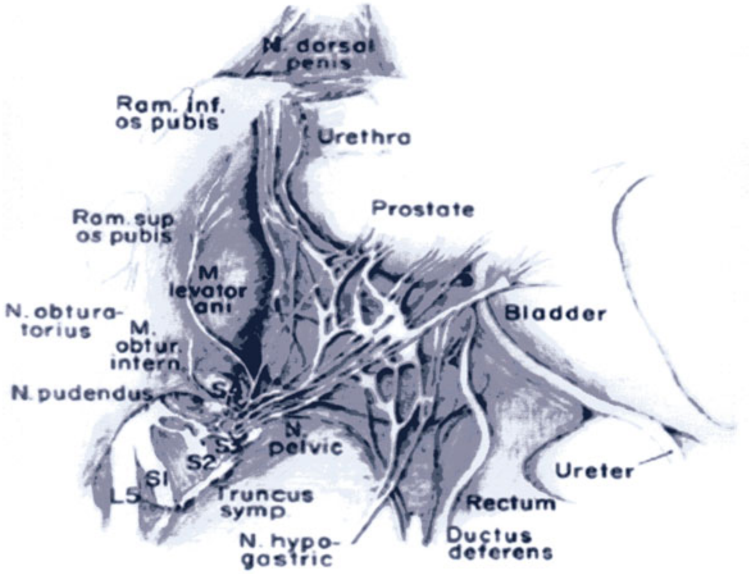

Fig. 4.2 Anatomic drawing depicting the path of the cavernous nerves taken with permission from the authors. Walsh, P.C. and Donker, P.J., Impotence following radical prostatectomy: insight into etiology and prevention. J Urol, 1982. 128(3): p. 492–7

nerves that emanate from the spinal cord, S2–S4, through the hypogastric plexus past the tips of the seminal vesicles along side the rectum and then along the posterolateral aspect of the prostate between the true capsule and the lateral prostatic fascia finally piercing the urogenital diaphragm just posterior and lateral to the urethra (Fig. 4.2). Widespread popularization of this knowledge has facilitated our ability to preserve the cavernous nerves. Since this landmark study other studies have led to the discovery of additional findings potentially related to the physical preservation of the nerves.

Takenaka and associates have contributed several papers regarding male pelvic neuroanatomy. In two studies, they performed gross and histologic dissections of male cadavers defining the cranial and caudal paths of the cavernous nerves [9, 10]. With regard to the origin of the nerves, they determined that in most individuals the traditional neurovascular bundles contain few parasympathetic nerve components proximal to the bladder–prostate junction. Instead, parasympathetic nerve branches configured in a "spray-like" distribution approach the dorsolateral prostate at least 20 mm below the bladder–prostate junction.

In another paper, Takenaka and associates describe the presence of autonomic ganglion cells which were postulated to have an effect on the return of potency [11]. Ganglion cells were found throughout the surfaces of the pelvic viscera including the hypogastric plexus, the seminal vesicles, the levator ani muscle, the bladder, and the prostate. The NVB also contained many ganglion cells. The number and distribution varied a great deal and the authors' speculated this variability might contribute to susceptibility or resistance to impotence. However, it has historically been recognized that these ganglia correspond to the end organs they are adjacent to and don't have any bearing on potency whatsoever [12]. In fact, Alsaid et al. described the presence of various types of nerve fibers within the NVBs in the male fetus. Using 3D modeling, they found that multiple types of nerve fibers originated from the inferior hypogastric plexus, providing cholinergic, adrenergic, and sensory innervation to seminal vesicles, vas deferens, prostate, and urethral sphincter in a fan-like formation [13]. Interestingly, similar studies by Menon and Tewari have shown that the pelvic plexus is located [14, 15] midway adjacent to the tip of the seminal vesicle. These authors like Takenaka also described the appearance of multiple autonomic ganglia in the vicinity of the cavernous nerves. Both describe interconnections between the left and right neurovascular bundles along the anterior rectal wall within Denonvillier's fascia. Unlike Takenaka, however Tewari and associates describe cavernous branches of the pelvic plexus coalescing to form a more traditional "bundle" that runs within a triangular area (the neurovascular triangle) between the inner and outer layers of the periprostatic fascia and Denonvillier's fascia. The inner layer of periprostatic fascia (also called as the prostatic fascia) forms the medial vertical wall of this triangle; the outer layer of periprostatic fascia (also called as lateral pelvic fascia) forms the lateral wall, and the posterior wall of this triangle is formed by the anterior layer of Denonvillier's fascia. This triangular space is wide near the base of the prostate and becomes narrower near the apex. Menon has described a belief that additional nerves important for sexual function exist within periprostatic fascia that covers the lateral and anterior surface of the prostate that he aptly named the Veil of Aphrodite. The authors acknowledge they have not traced these nerves to the corpora cavernosa. They also hypothesize that because the plane of dissection is away from the cavernosal nerves other factors such as decreased traction, avoidance of thermal injury, and preservation of extra blood supply may play a role in preservation of nerve function.

In 2005, Costello and associates reported a detailed description of the plexus of nerves running within the NVB [16]. They found multiple nerve branches that emanated from the hypogastric plexus and spread significantly, with up to 3 cm separating the anterior and posterior nerves (Fig. 4.3). Similar to Menon, Costello noted that the NVB courses along the posterolateral border of the prostate within the bounds of lateral pelvic fascia, the pararectal fascia, and Denonvillier's fascia. In distinction to Menon and associates, they felt that the nerves located within the Veil of Aphrodite primarily innervate the prostate. This finding was more recently confirmed by Ganzer et al. who used immunohistochemical staining to ascertain the type and distribution of the periprostatic nerves. They found that parasympathetic (pro erectile) nerves were most prevalent dorsolaterally (within the true neurovascular bundle) with minimal percentages of fibers more anterolaterally on the prostate [17]. Similar to Takenaka, Costello found that the nerves converge mid prostate forming a more condensed bundle and then diverge again when approaching the prostatic apex where they divide into numerous small branches that descend along the posterolateral aspect of the membranous urethra, before penetrating the corpora cavernosa.

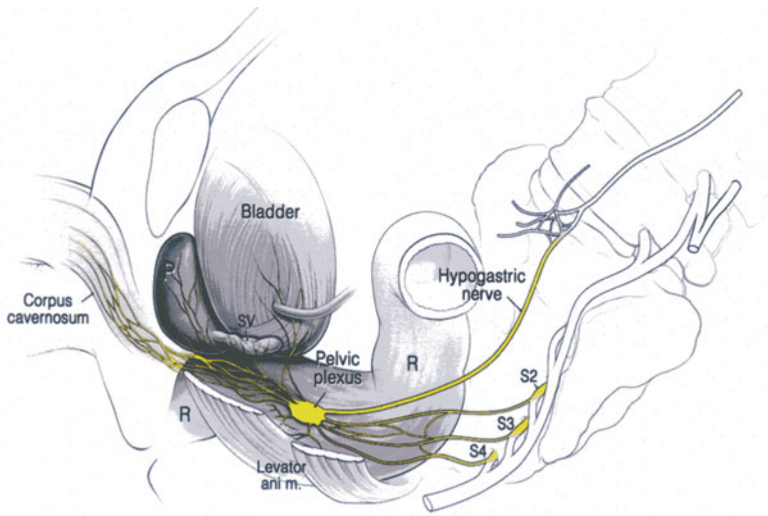

Fig. 4.3 Anatomic drawing of the path of the cavernous nerves based on cadaveric dissection. Note the posterolateral position of the neurovascular bundle in relation to the prostate. The nerve fibers more anterior on the prostatic surface do not go to the corpora cavernosum. Taken with permission from the authors. Costello, A.J., M. Brooks, and O.J. Cole, *Anatomical studies of the neurovascular bundle and cavernosal nerves*. BJU Int, 2004. 94(7): p. 1071–6

From the surgeon's perspective there are several take-home messages to be gained from these important anatomic studies: First, the most obvious and helpful landmark to identify the neurovascular bundle is the prostatic vascular pedicle (PVP). Transection of the PVP should be performed with care. This is the first point where surgical trauma caused by thermal injury (excessive cautery), traction (via dissection for clip placement), or direct transection risks collateral injury to the NVB. The authors share several helpful observations regarding the minimization of cautery and traction later in this chapter. Once the PVP is transected the NVB is posterior and lateral to the prostatic surface running along the side of the rectum extending from the base to the apex. It is our opinion that the inadvertent permanent transection of the NVB occurs most frequently at the apex slightly posterior and lateral to the urethra where the structure is most delicate. Dissection of tissues anterior to the urethra (dorsal venous complex and puboprostatic ligaments) does not risk NVB injury.

Pathophysiology of Cavernous Nerve Injury

With the above information regarding the anatomy of the neurovascular bundles in mind it is also important to consider the microscopic anatomy of these nerves and how this relates to nerve injury and healing. The peripheral nervous system is comprised of somatic motor nerves, sensory nerves, and autonomic nerves (parasympathetic or sympathetic). The parasympathetic nerves are responsible for erectile function. Although the name “autonomic” implies that this system functions in an isolated manner, the autonomic system relies on sensory information received from both the peripheral and central nervous system [18]. Erectile function is governed by the parasympathetic nervous system (PNS). All parasympathetic pathways consist of two neurons (the preganglionic neuron and the postganglionic neuron). The cell body of the efferent preganglionic neurons originates in the gray matter of the spinal chord and leave the central nervous system via the spinal nerves. In the case of erectile function, the preganglionic parasympathetic nerves leave the spinal chord via the S2–S4 spinal nerves and then travel to the pelvic plexus. It is generally recorded that parasympathetic preganglionic nerves are long and synapse within a second ganglion on the organ (i.e., corporal bodies) and then the postganglionic fibers travel via short nerves (2–3 mm) to innervate the penis. Currently, there is controversy regarding this matter, however, ultrastructural and functional studies of the cavernous nerves in rats have shown that the cavernous nerves contain both myelinated and nonmyelinated fibers and that most myelinated fibers within the cavernous nerves are preganglionic parasympathetic fibers [19]. Hence, it is reasonable to say that this also most likely the case in humans.

Preganglionic fibers are myelinated and postganglionic fibers are nonmyelinated. The distinction between pre and postganglionic parasympathetic fibers anatomically is that each individual axon of a preganglionic fiber is associated with a single Schwann cell that envelopes it in a myelin sheath whereas for postganglionic fibers multiple axons are enveloped by a single Schwann cell. *It is important to note that both myelinated and nonmyelinated nerves have the ability to heal and regenerate because they are both housed by Schwann cells and can both heal and regenerate* as described later [20, 21].

Definitions of Nerve Injury

During World War II, Sir Herbert Seddon defined peripheral nerve injuries into three categories of brutality [3]. The least severe, designated neurapraxia was considered a mild injury due to nerve contusion from blunt impact or stretch injury to the nerve without structural damage (Fig. 4.4, top). This concussion-like state is caused by damage to the perineural blood supply and results in a short-lived conduction block allowing full recovery in days to weeks.

The second level of injury, axonotmesis is the result of axonal disruption and Wallerian degeneration; however, the perineurium is preserved and the nerve or axon retains the ability to regenerate from the point of injury to the end organ provided the perineurium remains intact (Fig. 4.4, middle). Again, both myelinated and unmyelinated fibers can undergo axonal sprouting and regenerate [20]. Notably, regrowth of the axon advances at ≈1 mm/day or 2.54 cm/month and recovery takes 8–24 months. In this case the role of the microenvironment within which the axons are regenerating is critical and may be a potential source for augmentation by the addition of chemical or physical agents that promote regeneration.

The most severe of the three classifications and the most grim nerve injury to overcome is neurotmesis, a severe injury or a laceration that completely cuts across the axon and

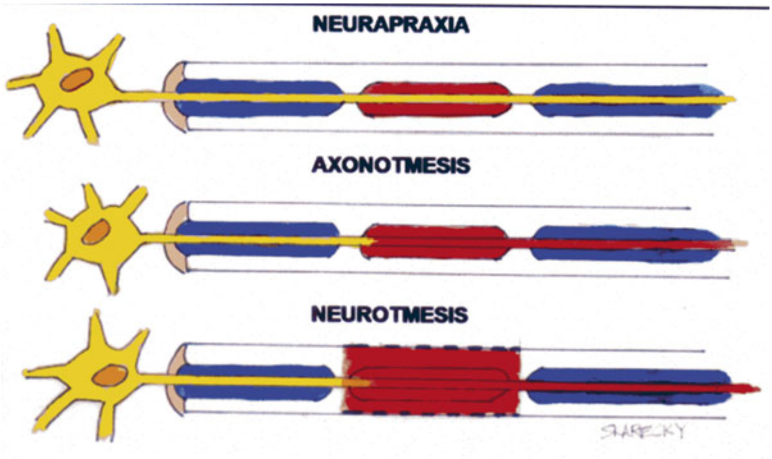

Fig. 4.4 Drawing depicting the three types of nerve injury described by Sir Herbert Seddon

perineurium, providing no scaffolding for regrowth of the axon, and generally resulting in a neuroma or scar (Fig. 4.4, bottom). With this more severe form of injury there is a greater chance of neuronal death and hence little capacity for regrowth of the axon.

Thermal Mechanisms for Cavernous Nerve Injury

The use of thermal energy to control the PVP is now a well-recognized mechanism of NVB damage as the NVB resides millimeters posterior-lateral to the PVP. In the early years of robotic and laparoscopic prostatectomy, the vascular pedicles were most commonly controlled with various types of cautery. Typically bipolar cautery would be used followed by cutting with scissors. This approach of cauterizing and cutting leads to substantial desiccation and thermal spread which in turn caused varying degrees of nerve injury. Early in our experience, we reported the adoption of a thermal technique to control the PVP using temporary occlusion of the PVP with bulldog clamps followed by suture ligation [22]. By simply avoiding cautery, potency at 3 months increased from 8 to 38 % [23, 24]. Remarkably, there was also a slow and steady recovery of potency in the cautery group over 2 years[25]. The best explanation for this delay was that although some injury to the NVB occurred, the injury was not permanent and the cavernosal nerves regenerated and potency was recovered (Fig. 4.5).

The reasons for the 2-year period needed for recovery of erections is rooted in basic and clinical science. Temperature increases of just 4 °C (heating tissue from 37 to 41 °C) can produce neural injury [26, 27]. Reaching temperatures of 45–60 °C causes more damaging protein denaturation and temperatures above this level cause protein coagulation which induces cell death [26]. It has been demonstrated that electrocautery produces temperature elevations and thermal energy effects beyond

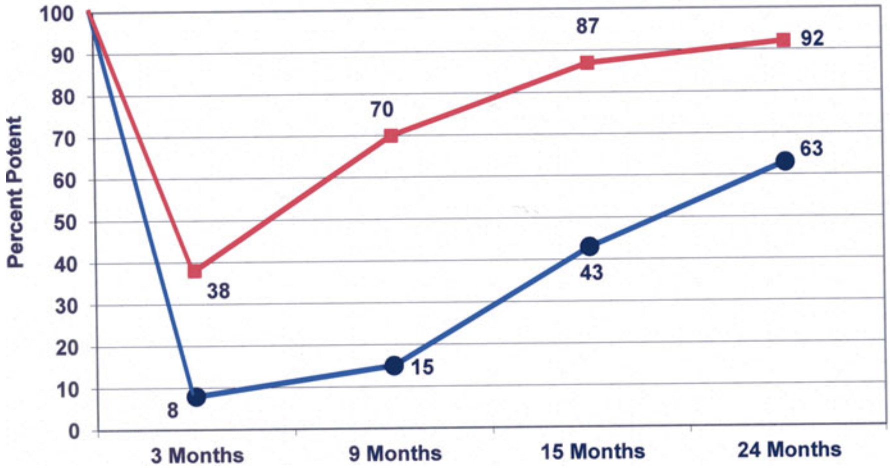

Fig. 4.5 Potency rates for patients in the author's series at 3, 9, 15, and 24 months following robotic radical prostatectomy. The *blue line* represents patients for whom cautery was used to secure the prostatic vascular pedicle with obvious resultant injury, however at 2 years recovery was substantial. The *red line* represents the authors "cautery free" technique to secure the prostatic vascular pedicle

the site of cautery. In essence standard laws of thermodynamics apply. Donzelli and associates demonstrated that both monopolar and bipolar cautery cause thermal injury to nearby neural tissue [28]. The importance of thermal injury to the cavernosal nerve was demonstrated in a landmark paper by Ong and associates that described the effects of thermal injury in a canine model [29]. In this study, monopolar electrocautery, bipolar electrocautery, and harmonic shears all resulted in a >95 % decrease in cavernosal pressures to standard suture ligatures for unilateral cavernosal nerve dissection. Histologic studies comparing the individual groups confirmed an increased amount of inflammation associated with the use of heat. Mandhani and colleagues measured temperature changes at the NVB with monopolar and bipolar cautery during robotic prostatectomy. The authors found that both mono and bipolar electrocautery raise temperatures to an equivalent degree but that monopolar cautery appears to coagulate more efficiently and hence shorter periods of application at lower temperatures are necessary [30]. Another interesting study by Khan and associates demonstrated the thermodynamic impact of heat sink effect by adjacent arteries and veins (Fig. 4.6). These authors demonstrated that thermal energy applied adjacent to inferior epigastric vessels had minimal temperature spread [31]. Zorn and colleagues also nicely demonstrated that the pathological findings of thermal spread to adjacent tissues can be measurably reduced by using cold irrigation concomitantly with cautery [32]. The authors have found that using cold irrigation to limit thermal spread of monopolar cautery has allowed us to reduce the amount of traction needed during PVP transection. Instead of applying clips or suture ligatures to the PVP, the authors simply recommend suture ligation or if the pedicle is too thick to simply cut the PVP. The highly magnified view presented during robotic

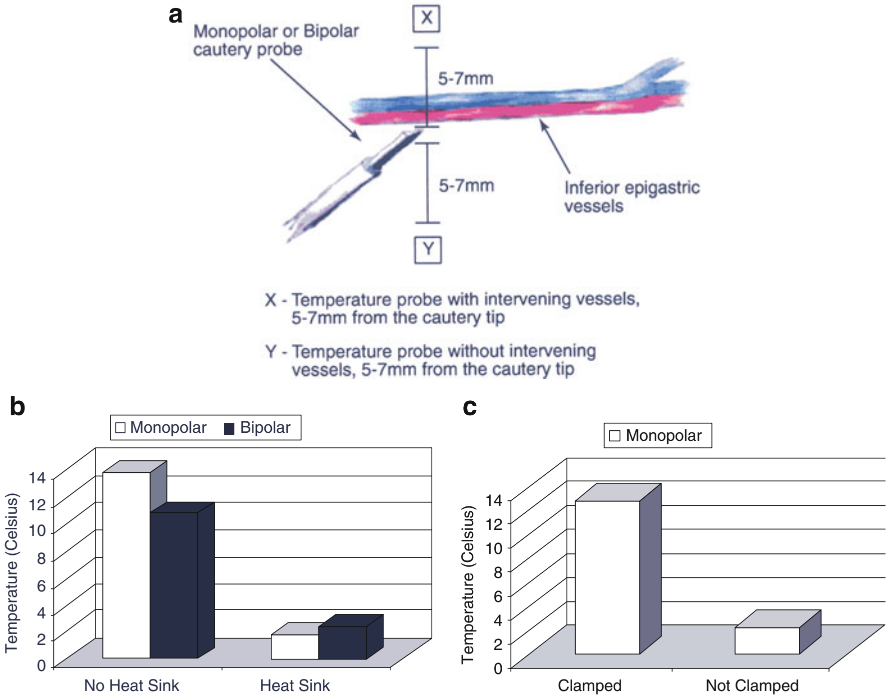

Fig. 4.6 (**a**) Application of monopolar or bipolar cautery at 20 W with (*x* distance) and without (*y* distance) intervening inferior epigastric vessels. (**b**) With interposing inferior epigastric vessels (heat sink), thermal spread is markedly reduced at 5–7 mm from monopolar or bipolar cautery probe. (**c**) With the interposing inferior epigastric vessels clamped, thermal spread across the vessels is markedly increased at 5–7 mm from the MP cautery probe, eliminating the 'heat sink' affect. Figures taken from: Khan, F., et al., *Spread of thermal energy and heat sinks: implications for nerve-sparing robotic prostatectomy*. J Endourol, 2007. 21(10): p. 1195–8

prostatectomy along with copious cold irrigation allows individual bleeders to be identified. The use of very judicious spot monopolar cautery can be used to control these bleeders while minimizing thermal spread to the NVB.

Traction Mechanisms for Cavernous Nerve Injury and the Application of Minimally Invasive Traction (MIT)

From 2003 to 2005 the transition to a thermal technique for transecting the PVP during robotic prostatectomy was reported using temporary occlusion of the PVP with a bulldog clamp [23]. The development of "cautery free" techniques certainly enhanced potency outcomes compared to previous results with cautery. However, even with totally energy free surgery, at least 65 % of men take 9–15 months to recover erectile function [8]. The reason for this phenomenon must be injury due to traction [33]. There are competing goals during radical prostatectomy. The principles of "traction and countertraction" are important in terms of surgical exposure and performing and anatomically correct dissection. On the other hand, these principles are in direct opposition to the neurosurgical premise of "dissecting the tumor off of the nerve." This basic premise of neurosurgery has been known and taught for decades to avoid undue nerve injuries during procedures across all surgical disciplines.

Excessive traction on the neurovascular bundle must have profound unintended consequences as the NVB is quite fragile. Traction injury may occur by direct stretching of the nerves or because of microvascular bleeding in the perineurium leading to secondary infiltration, compression, and inflammation. Figure 4.7 depicts the next technical/surgical hurdle to overcome for preserving potency postradical prostatectomy. It is the mastery of Minimally Invasive Traction (MIT). Similar to other specialties in which "dissecting the tumor off of the nerve" is instilled from day 1, we as robotic surgeons must turn our concentration toward minimizing traction during ligation of the PVP and dissection of the NVB. This remains a particularly challenging dissection for the experienced surgeon and a formidable obstacle for the novice.

Much has been written about avoiding cautery during NVB preservation. Indeed, a 2012 consensus RARP group recommended that the simplest solution is to avoid thermal energy altogether near the NVB [34]. Although complete avoidance of cautery has its stated advantages this method necessitates the use of clips or ligatures which again requires tissue on tension to apply. How then does one avoid tension and minimize damage from cautery. It is possible to minimize traction by simply cutting through the PVP with cold scissors. With regard to control of bleeding when this is done, there is evidence that if the laws of thermodynamics are observed, cautery can be applied while keeping thermal spread to a minimum [31]. This is accomplished by using low wattage, short bursts of cautery performed in a pinpoint fashion and maximizing distance from the NVB. The addition of cooled saline irrigation may further

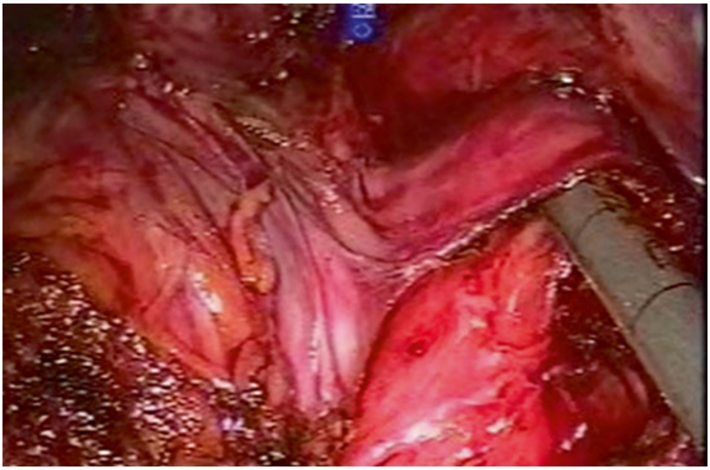

Fig. 4.7 For mastery of Minimally Invasive Traction (MIT), robotic surgeons must turn their concentration toward minimizing traction during ligation of the PVP and dissection of the NVB, by "dissecting the tumor off of the nerve," and avoid the opposite as shown in this figure

limit the spread of heat from surgery [32]. It remains to be seen if such modifications will lead to improved outcomes but certainly we must place emphasis on these basic neurosurgical principles and adapt our technique to minimize nerve injury.

Nerve Redundancy

A very intriguing and important question is what evidence exists regarding the critical volume or percentage of nerve required for preservation of potency? Simply put: What impact does widely excising one of the NVBs have on potency? The fact that there is any recovery speaks to "systems redundancy." We compared potency outcomes in patients in whom we spared both nerves (BNS) to those who had one excised UNS [35]. Also queried was the qualitative recovery following preservation of one versus two nerves, i.e., a doubling of nerve volume. Definitions of unilateral nerve sparing were quite specific; it only included patients with a wide excision of one nerve, which was confirmed pathologically. The group of men undergoing bilateral nerve preservation had a 2-year recovery rate of 92 % whereas men having just one nerve preserved recovered 80 % of the time. So with a 50% reduction of nerve tissue the potency rate was only diminished by approximately 15 %. Qualitatively for the 80% of men reporting successful erections after UNS the average postoperative IIEF-5 scores were not significantly different (UNS 22.0 vs BNS 21.0).

Similar findings have been reported by Walsh and colleagues [36]. They reported that 69 % of men potent before RP who had unilateral wide excision were potent after RP, compared to 85 % who had BNS. Kundu and associates reported a similar trend in overall potency rates at 18 months, of 53 and 76 % after UNS and BNS RP, respectively [37]. What is consistent across all these reports is that doubling the volume of nerve tissue improved potency rates by about 1.15–1.4×. This finding supports redundancy and also speaks against using extreme measures such as intrafascial nerve-sparing dissection. For example, intrafascial dissection might preserve another 5 % of nerve tissue but, considering the data earlier, the benefits to increased potency would only rise minimally if at all.

Testosterone

The negative impact of hypogonadism has been called "The Dark side of Testosterone Deficiency" and manifests as cardiovascular and stroke disease, Type 2 diabetes, metabolic syndrome, central obesity, lack of energy, and erectile dysfunction [38]. Defining hypogonadal males is usually a combination of symptoms and testosterone levels below either 350 or 230 ng/dl [39]. However, calculated free testosterone appears to be much more accurate in predicting clinically relevant issues or complications [40]. There is growing evidence that having higher FT levels predict favorably on the risk of low pathologic Gleason grade and faster recovery of sexual function (Fig. 4.8) [41]. In our

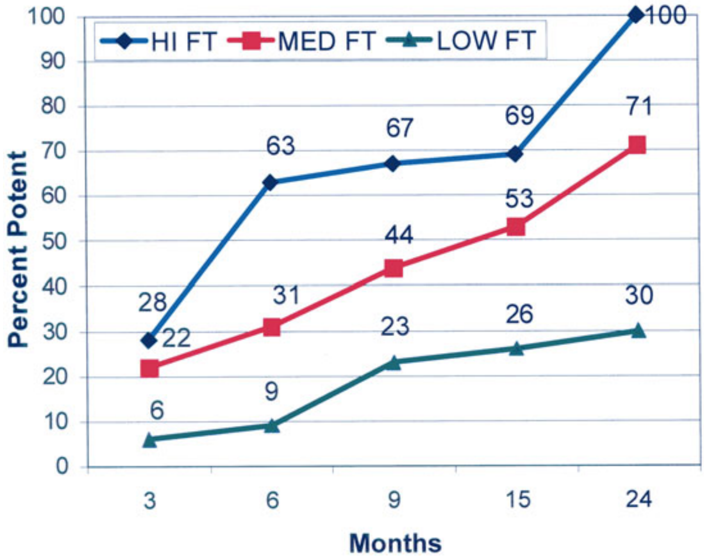

Fig. 4.8 Potency of patients in the authors series with follow-up of 24 months stratified by low (*green*), intermediate (*red*), and high (*blue*) serum-free testosterone levels following nerve-sparing robotic radical prostatectomy

opinion testosterone levels should be checked pre and postoperatively and if free levels are low men should have a discussion regarding replacement.

Postoperative Prophylaxis for Erectile Dysfunction

In experimental models it has been shown that injury to cavernous nerves in rats leads to endothelial cell apoptosis, decreased nitric oxide levels, and hypoxia leading to fibrosis and loss of smooth muscle in the corpora cavernosa [42–45]. In humans, there is clear evidence that fibrosis and loss of smooth muscle occurs and that vasculogenic effects occur as a result. Mulhall and associates first noted that arterial insufficiency occurs in approximately 50 % of patients following RP and does not improve within a year of surgery. In addition, approximately 50 % of patients developed venous leak 1 year following surgery which was also associated with a decreased return of erectile function [46]. Montorsi and associates reported that 6 months following surgery spontaneous erection occurred in 67 % of patients who performed self-injection with PGE-1 compared to 20 % in patients that did not use injection therapy. Only 17 % of patients who injected PGE-1 developed venous leak by Doppler ultrasound criteria versus 53 % of patients who did not [47]. Similar findings have been reported both for PGE-1 urethral suppositories [48] (Alprostadil, Vivus) and vacuum devices [49].

In 2003 Padma-Nathan and associates in a randomized prospective study reported that 27 % of 51 patients who were potent prior to bilateral nerve-sparing radical retropubic prostatectomy who took sildenafil at bedtime for 9 months regained "full" potency versus only 4 % of patients that did not [50, 51]. These findings may possibly be explained by Schwartz and associates who examined the effect of sildenafil on the smooth muscle content of the corporal bodies after RRP. In this study, patients were divided into two groups: one receiving 50 mg every other night for 6 months following surgery and the other 100 mg. The higher dose group had a statistically significant increase in smooth muscle present on postoperative biopsy [52]. In similar fashion, Montorsi and colleagues in 2014 also confirmed an advantage to men who prophylactically took tadalafil in a randomized trial [53].

Although the cumulative knowledge regarding novel prophylactic treatments to hasten the return of erectile function in men following RRP is encouraging, there is no regimen that is clearly superior. Further, there is no consensus among experts with regard to the most effective agent or combination of agents to use. We currently recommend 5 mg of tadalafil nightly starting on the first postoperative day for all patients. For those patients who are highly motivated, PGE-1 self-injection three times per week is also offered.

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