Testicular Pain Following Vasectomy: A Review of Postvasectomy Pain Syndrome

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Since the late 1970s the definition and etiology of chronic testicular pain following vasectomy has been evolving, as have the names for this syndrome, including postvasectomy orchalgia (Shapiro and Silber, 1979), late postvasectomy syndrome (Selikowitz and Schned, 1985), congestive epididymitis (Schmidt and Free, 1978), chronic testicular pain (McMahon et al, 1992), and postvasectomy pain syndrome (McCormack and LaPointe, 1988). Today, the syndrome is generally recognized by the term post-vasectomy pain syndrome (PVPS). Although the mechanism has not been proven, a number of studies have shown changes in the histology of the epididymis and the testis following vasectomy. Patients with PVPS generally present with orchalgia; pain with intercourse, ejaculation, or both; pain with physical exertion; and tender or full epididymides (Nangia et al, 2000). The theory that these symptoms are caused by infection has long since been discarded, due to the lack of response to antibiotics in these patients and absence of acute infection when epididymal and vasal sections are removed during surgery and analyzed histologically (Selikowitz and Schned, 1985; Chen and Ball, 1991). Instead, histologic studies of samples collected during vasovasostomy or epididymectomy have demonstrated a chronic inflammatory process that begins to explain the development of PVPS.

Anatomic Review
Each component of the ejaculatory system proximal to the vas deferens seems to be affected in some way by vasectomy. It has long been believed that many of these structures, including the efferent ducts and the epididymis, were simply collecting areas for sperm and made little or no contribution to the process of ejaculation or sperm maturation. On the contrary, these structures are key to maintaining the viability of the ejaculatory system in patients after vasectomy (Lipshultz et al, 1981). The following is a brief review of these important structures.

Sperm are continually produced following puberty and continuing through adulthood. Adult testes, weighing on average 16.9 ± 1.2 g, continually produce about 4.25 million spermatozoa per gram. Studies suggest, however, that only 50%–60% of the spermatozoa produced are available for ejaculation (Alexander, 1972; Amann and Howards, 1980). Ejaculatory volume is approximately 3 mL, with an average of 100 million spermatozoa per milliliter (Sigman and Howards, 1998).

From the testes, sperm travel through the efferent ducts into the epididymis, where maturation is completed. These 2 structures are far from being simple storage compartments for sperm in transit to the vas deferens. The efferent ducts and proximal epididymis have an active role in moving sperm into the body of the epididymis via smooth muscle contraction and ciliary motion during emission and ejaculation (Risley, 1963). In addition, according to a study by Alexander (1972), secretory products are added to the sperm while particles and excess fluids are absorbed as demonstrated by the uptake of colloidal particles, peroxidase, and trypan blue.

The epididymis is a highly specialized organ with regional differences in function. Its importance in fertility is demonstrated by the fact that spermatozoa taken from the testis are inactive and unable to independently fertilize an egg (Alexander, 1972). It is only within the epididymis that sperm take on their mature form. Its other functions include recycling and clearance of degenerating sperm and fluid management. As sperm pass through the efferent ducts and into the epididymis, many are nonviable or have malformations and must be removed. It has been estimated in animal studies that 40%–50% of sperm produced are reabsorbed before they reach the vas deferens (Alexander, 1972). The majority of these degenerating sperm are present within the body of the epididymis but few are present in the ejaculate, suggesting that the caudal epididymis is the site for sperm disposal. The precise mechanism behind this is not known, although phagocytes are believed to play a role as their numbers increase in the tail of the epididymis after vasectomy (see Post-vasectomy Changes).

The vas deferens is composed of several layers, including the adventitia, tri-laminar muscle, and mucosa surrounding a lumen of 0.5 mm (Corson, 1981). That the luminal diameter is smaller than the wall thickness emphasizes the propulsive function of the vas deferens. A rich blood supply feeds into the adventitial layer along
with branches of sympathetic nerves. These nerves stimulate wavelike contraction of the vasal musculature in response to norepinephrine stimulation (Corson, 1981). Disruption of the vas deferens through manipulation or transection results in changes in the mucosa, muscular layers, and coordination of contraction (Shandling and Janik, 1981; Janik and Shandling, 1982; Sandhu et al, 1992). The studies by Janik and Shandling in rats showed that instrumental manipulation (grasping with forceps, clamping with a hemostat) of the vas deferens leads to damaged muscle layers and abscess formation with minimal repair of the muscular layers at 6 months. Although infertility is the most feared complication of manipulatory trauma or transection of the vas deferens, diminished or retrograde ejaculation may occur as well (Janik and Shandling 1982).

Postvasectomy Changes

A number of surgical techniques exist for vasectomy but they can be divided into the 2 main categories of open-ended and closed-ended. Open-ended vasectomies involve leaving the scrotal end of the vas deferens open to promote the release of intraepididymal pressure through the formation of a chronic inflammatory sink or a sperm granuloma. The formation of the granuloma tends to occur early postoperatively. Closed-ended vasectomies use surgical clips, ties, or cautery to transect the vas deferens and seal both the proximal and distal stumps, leading to an immediate increase in luminal pressure. The rapid pressure increase often overwhelms the strength of the epididymal or vasal wall, leading to such things as epididymal blowouts, vasitis nodosa, and sperm granulomas, although these are typically late findings. The classic postvasectomy findings can be divided into early, intermediate, and late changes. For ease of discussion, the remainder of the article will focus on changes observed after closed-ended vasectomy, because these are most common.

Early Postvasectomy Changes—In adults, transection of the vas deferens causes increased luminal fluid pressure. This increase in pressure is transmitted to the source of the fluid—the testis, efferent ductules, and the head of the epididymis. Each of these areas contributes fluid to the sperm in transit to the ejaculatory ducts. Studies by Alexander (1972) in rhesus monkeys and those by Jarow et al (1985) in human testicular biopsies showed that several years after vasectomy, a number of changes take place in the normal ciliated columnar cell-lined efferent ductules. Initially, the diameter of the ducts increases 2 to 4 times its original size to counteract the increase in fluid pressure (Alexander, 1972; Jarow et al, 1985; Matsuda et al, 1996). Fluid absorption is increased, particularly in the efferent ducts, where 90% of excess fluid is reabsorbed (Nistal et al, 1999). Tubular histology changes such that many of the ciliated cells present in the ductules disappear. The basal lamina has also been shown to thicken by 2 to 3 times its original depth in response to the deposition of antibody-complement complexes and collagen (Alexander, 1972; Jarow et al, 1985). These compensatory mechanisms seem to delay significant pathology, but due to the ongoing production of sperm, further alterations often take place to avoid permanent testicular dysfunction.

Obstructive effects on spermatogenesis seem to be minimal (Linnet, 1983; Nistal et al, 1999; Meng et al, 2001). Two recent studies reported that after vasectomy, spermatogenesis continues unabated with increasing fluid pressure forcing sperm into the dilated, congested epididymis (Nistal et al, 1999; Meng et al, 2001). These studies demonstrated that even in those patients with congenital bilateral absence of the vas deferens (CBAVD), only 12%–21% had hypospermatogenesis. Those patients who did exhibit decreased sperm production were found to have a greater occurrence of varicoceles and other factors affecting sperm survival. The remaining patients with CBAVD had what the authors described as “late sloughing of primary spermatocytes,” meaning that spermatogenesis is normal but the spermatocytes tend to die late in maturation (Meng et al, 2001). Patients with a history of obstruction secondary to vasectomy or herniorrhaphy had a high percentage of these late sloughing primary spermatocytes as well, suggesting that the increase in pressure, although it does not seem to affect spermatogenesis, may alter the maturation and survivability of developing sperm (Nistal et al, 1999; Meng et al, 2001). It has been postulated that the decrease in survivability is secondary to the loss of Sertoli cells, which are believed to have an increased susceptibility to the rising luminal pressures (Nistal et al, 1999).

Intermediate Postvasectomy Changes—At this point, the fluid within the obstructed ejaculatory system overwhelms the dilatory and absorptive capacity of the epididymis and efferent ducts. In response, macrophages begin to infiltrate the epididymis and accumulate in high numbers compared with their seemingly rare appearance before vasectomy. Alexander (1972) studied the long-term effects of vasectomy in rhesus monkeys and found that before and 1 to 3 months after vasectomy, few if any phagocytic cells were present within the epididymis. However, at 3 months after vasectomy the number of macrophages laden with phagocytized sperm had drastically increased throughout the epididymis. This suggests that in the normal epididymis, dead and degrading sperm are taken up through pinocytosis by the epithelial cells lining the efferent ductules and epididymis. When obstruction occurs, the task of reabsorbing the sperm overwhelms the epithelial cells; therefore, macrophages are recruited from the circulation to aid in their digestion and...
clearance. It has also been speculated that there is concurrent breakdown of epithelial tight junctions with subsequent leakage of sperm into the interstitium (Linnet, 1983). The presence of large numbers of phagocytes and the possibility of interstitial leakage sets up an autoimmune state as chronic inflammatory cells digest spermatozoa and present antigens for antibody production (Alexander, 1972; Linnet, 1983).

At 1 year after vasectomy, 60%–70% of men have antisperm antibodies present in their serum (Linnet and Hjort, 1977; Linnet et al, 1981). Significant controversy exists over possible side effects of these circulating antibodies, however, that issue is beyond the scope of this paper. Sperm have not been encountered in fetal life due to the blood-testis barrier, which primes the body for antisperm antibodies in the situation of extravasation or antigen presentation by phagocytic cells (Linnet, 1983; McCormack and LaPointe, 1988). Macrophages, which have been shown to increase in the epididymal lumen with obstruction, are antigen presenting cells with the ability to stimulate T cells and secondarily B cells, causing them to begin antibody production. Alexander’s studies (1972) of vasectomy in rhesus monkeys showed increasing levels of antisperm antibodies with time, including antibodies present within epididymal fluid. At 3 years after vasectomy nearly all the sperm present in the efferent ducts and the epididymis were agglutinated. Immunofluorescence studies demonstrated antibodies binding the agglutinated sperm as well as antibody-complement complexes present in the basal lamina, whereas no such complexes were observed in normal control monkeys. Although this was a common occurrence in the rhesus monkey, human studies show that antisperm antibodies occur within the epididymis in only 7%–30% of postvasectomy patients (Linnet and Hjort, 1977; Linnet et al, 1981). This suggests that antisperm antibodies do not have a major role in post-vasectomy pathological changes, however, they may play an important role in the pathology of PVPS.

Late Postvasectomy Changes—The late postvasectomy changes, including vasitis nodosa, epididymal blowouts, and sperm granulomas, represent the body’s effort to spare the testicle from damage secondary to increasing pressures (Schmidt, 1979; Shapiro and Silber, 1979; Taxy et al, 1981). Although these alterations may occur earlier in some (ie, sperm granulomas in open-ended vasectomy patients), the majority occur late, after all efforts to manage the increasing pressure have been exhausted. Generally, these lesions are completely benign and are asymptomatic. It has been shown that an absence of these lesions, particularly sperm granulomas, may predispose patients to PVPS (Shapiro and Silber, 1979; Taxy et al, 1981).

The first lesion to develop is vasitis nodosa, which is formed by a proliferation of vasal epithelial cells within the adventitia and surrounding interstitium in response to fluid and sperm dissection into the vasal wall. They tend to be located at the site of ligation of the proximal vas deferens, however, they have been demonstrated in men with primary infertility (Taxy et al, 1981). A study by Taxy et al (1981) of subclinical pathologic findings following vasectomy found that vasitis nodosa was present in 66% of the patients who were studied. Nearly two-thirds of these patients also had sperm granulomas.

Once sperm have dissected through the muscular wall of the vas deferens and into the adventitia, the next step is extravasation into the interstitium. As sperm are broken down by macrophages and lymphocytes, sperm components stimulate antigen presenting cells which, in turn, initiate the release of cytokines that activate branches of the chronic inflammatory pathway. Histiocytes are the primary cell present in these lesions, which tend to grow in response to the continual flow of sperm and assist in the function of sperm absorption by concentrating a large number of phagocytic cells. Activation of fibroblasts via cytokine release stimulates fibrosis, and a sperm granuloma is formed.

Sperm granulomas also form in response to leakage of sperm secondary to epididymal blowouts (Shapiro and Silber, 1979). In some patients, the increasing pressure overwhelms the walls of the epididymal tubules before the thick muscular wall of the vas. Similar to vasitis nodosa, this leads to sperm leakage into surrounding interstitium and sperm granuloma formation. Unilateral epididymal blowouts occur in 10% of patients after vasectomy within 10 years. Bilateral ruptures are seen in 50% of patients more than 10 years after vasectomy (Shapiro and Silber, 1979).

From the above-mentioned studies, it is clear that sperm granulomas occur frequently. Sperm granulomas form in 4%–60% of patients undergoing closed-ended vasectomy (Schmidt, 1979; Shapiro and Silber, 1979; Taxy et al, 1981; Chen and Ball, 1991; Myers et al, 1997; Nangia et al, 2000). This range is quite large due to the discrepancy among physicians and researchers describing these lesions. Clinically, the sperm granuloma is seen as a nodule (tender or nontender, depending on the physician’s definition) present on the epididymis or at the end of the proximal vas deferens. Histologically, they are characterized as a chronic inflammatory infiltrate surrounding a site of sperm extravasation and are mostly asymptomatic. Herein lies the difficulty in interpreting data in reporting the incidence of sperm granuloma. The histologic diagnosis of a sperm granuloma is by far the gold standard, because it eliminates the guesswork in differentiating between sperm granuloma, suture granuloma, vasitis nodosa, and fibrosis. However, vasal and epididymal biopsy is not a diagnostic possibility, therefore, clinical diagnosis of sperm granuloma must be ascertained.
through palpation of a nodule in the area of suspected sperm extravasation (ie, site of vasal ligation, or possible epididymal blowout) even though it may lead to a small number of false positive diagnoses.

These interesting lesions carry with them a certain degree of controversy as to whether or not they are truly benign. Shapiro and Silber (1979) reported their comparison of closed-ended vasectomy to open-ended vasectomy and found that 4% of patients with closed-ended vasectomy developed sperm granulomas. On the other hand, 97% of the patients who underwent open-ended vasectomy developed sperm granulomas. None of the patients with a clinical diagnosis of sperm granuloma had tenderness to palpation, however, one patient who did not develop a sperm granuloma did develop a case of congestive epididymitis after his closed-ended vasectomy. Unfortunately, long-term follow-up was not part of the study; however, the authors interpreted the results to conclude that sperm granulomas are entirely benign and their formation should be encouraged through the use of open-ended vasectomy to reduce the risk of PVPS. Another study by Moss (1992) helped confirm Shapiro and Silber’s conclusions. In this study, rates of PVPS were compared in 3081 patients with closed-ended vasectomy and 3139 patients with open-ended vasectomy. This study demonstrated that 6% of the patients with closed-ended vasectomy developed PVPS, whereas only 2% of patients with open-ended vasectomy did. At first glance this does not appear significant, but when combined with the presence of sperm granulomas in 97% of open-ended vasectomies in the study by Shapiro and Silber, the power of the numbers is clear. If nearly 100% of open-ended vasectomies result in sperm granuloma and only 2% of these patients develop PVPS, it is unlikely that the sperm granuloma is the cause for their pain. In fact, patients with PVPS generally do not have sperm granulomas, suggesting that PVPS is caused in part by the lack of a pressure vent (Shapiro and Silber, 1979; Chen and Ball, 1991; Nangia et al, 2000).

**Postvasectomy Pain Syndrome**

The pathophysiology underlying PVPS is a deviation from the natural progression of events within the ejaculatory system following disruption of the vas deferens. The definitive cause for PVPS is not known and may be the result of a number of subclinical processes occurring within the epididymis and further up into the spermatic cord. Theories have included epididymal congestion, painful sperm granulomas, vascular stasis, and nerve impingement.

The theory that a lack of a sperm granuloma causes PVPS would suggest that the late postvasectomy changes (ie, sperm granuloma, epididymal blowout, vasitis nodosa) occur at approximately 5 to 7 years, which may in fact, be an accurate statement. It would be assumed that up until this time, mechanisms such as tubular dilatation, basement membrane thickening, increased luminal phagocytosis, and so forth, had staved off the increasing epididymal pressure. Eventually, the pressure would become too great for the compensatory measures; increasing to uncomfortable levels due to the lack of a pressure valve or sperm granuloma. Although this is an attractive hypothesis, it suggests that PVPS is a natural progression of events in the estimated 5%–30% of patients who do not develop a sperm granuloma following vasectomy. However, only a small percentage of postvasectomy patients (less than 10%) develop PVPS. This suggests that other factors besides the lack of a sperm granuloma must predispose patients to the onset of epididymal congestion and pain.

It is likely that the anatomic derangement associated with vasectomy is responsible in part for PVPS. In postvasectomy patients, the epididymis is trapped in the middle of 2 opposing forces when intercourse or ejaculation occurs. As described above, the efferent ducts and the initial segments of the epididymis are lined with smooth muscle cells that contract during emission and ejaculation. The vas deferens also contracts in response to the associated noradrenergic and stretch stimuli. This results in movement of fluid from the testicle into the tail of the epididymis with simultaneous retrograde flow from vasal contractions into the caudal epididymis. Theoretically, this explains why the majority of epididymal fibrosis and blowouts in postvasectomy patients occur in the tail (Chen and Ball, 1991).

The autoimmune aspect of vasectomy may also play a role. Linnet and others have shown that 60%–70% of postvasectomy patients have serum antibodies to sperm (Linnet, 1977; Linnet et al, 1981). A smaller percentage (7%–30%) have antisperm antibodies present within the epididymis, correlating with high serum titers (Linnet, 1977; Linnet et al, 1981). Although it has been reported that serum anti-sperm antibodies have little effect on the heart and other organs, little has been done to examine the effects of antibodies present within the epididymis (Linnet, 1983). Alexander’s study (1972) with rhesus monkeys showed that at 3 to 5 years after vasectomy, antibodies to sperm were present within the epididymis. Via immunofluorescence studies, antibodies were shown to agglutinate sperm and activate the complement cascade, leading to immune complex formation and deposition in the basement membrane of the efferent ducts. In humans, these antisperm antibodies have also been shown to agglutinate sperm and even limit their ability to fertilize an egg (Linnet, 1983). Antibodies to both immunoglobulins A and G have been found within the epididymal fluid, suggesting that both local immunoglobulin produc-
tion and diffusion from the circulation into the epididymis occurs (Linnet et al, 1982).

As previously stated, many patients have been treated with various regimens, often to no avail. However, selected patients have responded to a reversal of the vasal obstruction via vasovasostomy, vasoepididymosotomy, epididymectomy, or open-ended vasectomy (Shapiro and Silber, 1979; Selikowitz and Schned, 1985; Chen and Ball, 1991; Myers et al, 1997; Nangia et al, 2000). For instance, Shapiro and Silber (1979) performed vasovasostomies on 6 patients with PVPS with complete relief of symptoms in all patients. In a larger study conducted by Myers et al (1977), 75% of their patients had complete resolution of PVPS following vasovasostomy or vasoepididymosotomy. Open-ended vasectomy is believed to alleviate the vasal obstruction by forming a sperm granuloma that chronically destroys sperm.

**Differential Diagnoses for Postvasectomy Pain**

In contrast to patients who present with delayed pain from congestion of the excurrent ductal system, chronic orchalgia in a patient after vasectomy with an early onset of pain or pain in the presence of a sperm granuloma expands the diagnosis to include such things as nerve impingement or injury, varicocele or hydrocele, infection, tumor, intermittent testicular torsion, inguinal hernia, referred pain, and psychogenic causes (Davis et al, 1990). Although each of these is a potential cause of pain, the majority can be ruled out based on a thorough history, physical examination, and urine analysis. However, in those patients without physical examination or laboratory findings the diagnosis is less clear, and neurogenic and psychogenic causes for the pain must be entertained. Particularly in patients with a history of spermatic cord manipulation (ie, vasectomy or inguinal hernia repair), the possibility of nerve injury is increased. Traveling with the spermatic cord are a number of nerves including the inguinal branch of the ilioinguinal nerve, the genital branch of the genitofemoral nerve, and the sympathetic and afferent nociceptive fibers accompanying the vas deferens (Starling et al, 1987). Injury or entrapment of any of these nerves may lead to chronic neuropathic pain.

Schmidt (1979) suggests that pain in the presence of a sperm granuloma in patients after vasectomy is due to nerve and vasculature impingement as the granuloma grows in response to the continual flow of sperm. He found that in a group of 154 patients presenting with pain and a sperm granuloma, 63 (40%) had similar symptoms of PVPS (pain with intercourse or ejaculation) and required surgical excision of the granuloma to relieve their pain. Shapiro and Silber (1979) found similar patients with PVPS who had painful granulomas and resolution of their pain with excision. Generally, these granulomas grow near the tail of the epididymis or around the vas deferens causing constriction of local nerves and blood vessels, leading to nerve compression, vascular stasis, and pain. Pain with ejaculation can be explained by increased pressure within the ejaculatory system, hence, within the sperm granuloma, causing further nerve compression (Schmidt, 1979).

Other patients present with an early onset of pain following their vasectomy likely due to a neuropathic cause as seen in patients with hernia repair postoperatively. The etiology of this pain is not entirely understood but is presumed to be caused by interruption of neurovascular bundles, specifically, those that travel along the length of the vas deferens and contain sympathetic nerves derived from the pelvic plexus and afferent nociceptive fibers (Cunningham et al, 1996). Disruption of these nerves may result in dysynergia of vasal contractions or scarring with subsequent neural compression resulting in pain.

The final subgroup of patients have a preexisting condition that causes their testicular pain. This may result from trauma, prior surgeries (ie, inguinal hernia repair), other urologic disturbances (ie, urinary tract stone, prostatitis), or from psychopathological conditions. For instance, patients with prior inguinal hernia repairs may have damage to branches of the ilioinguinal or genitofemoral nerves with radiation to the scrotum. Trauma to spinal nerves, the spermatic cord, and the testicle itself may predispose patients to episodes of testicular pain. Urinary tract stones and prostatitis may refer to the testicle (Davis et al, 1990). Finally, in patients with an atypical presentation and no identifiable cause for pain, a psychiatric evaluation should be sought before definitive management (Davis et al, 1990). This topic is extensive and, therefore, out of the scope of this discussion.

**Conclusion**

Postvasectomy pain syndrome is a poorly defined entity that although uncommon, presents a diagnostic and treatment challenge for physicians. Although the definitive cause for postvasectomy pain may be unclear, it is evident that traditional treatments such as antibiotics, excisional surgery, and chronic pain medication are unlikely to result in a successful outcome. Multimodal therapy, including nerve blocks, medical management, psychiatric referral, and in select patients, vasectomy reversal, are most likely to result in improvement in the quality of life for these men. Further investigations of vasectomy associated autoimmunity and the origins of neuropathic pain will hopefully provide insight into the etiology and focal therapy for these patients’ pain.

**References**


