

Priapism: pathophysiology and management

G. Liguori, S. Bucci, S. Benvenuto, C. Trombetta, E. Belgrano

Department of Urology, University of Trieste, Trieste, Italy

Summary

Introduction. Priapism is defined as a persistent erection of the penis not accompanied by sexual desire or stimulation and can be a urological emergency. There are three different types of priapism: low-flow priapism, high-flow priapism and recurrent priapism. Unfortunately, clinical guideline does not establish a fixed set of rules for the treatment of this condition.

Methods. This review combined an analysis of clinicopathologic reports as well as a summary of clinical and basic science investigations on the subject to date. Moreover, the proposed pathogenesis of priapism is reviewed, and a survey regarding treatment modalities is given.

Results. The prognosis depends on the type of priapism and the amount of time that passes before therapeutic intervention. It is important to distinguish between these conditions as the treatment for each is different. Low-flow priapism is a compartment syndrome with intracavernosal anoxia, rising pCO₂ and acidosis and urgent medical attention is mandatory to prevent erectile dysfunction. On the contrary in high-flow priapism intervention is not urgent and often unnecessary. Finally, recurrent priapism is a condition which is still not well understood and there is no standardised algorithm for the management of this condition.

Conclusions. Urologists should understand the importance of the disorder and be prepared to follow current principles of diagnosis and treatment to reduce or prevent its complications.

Keywords

Priapism • Penile erection • Erectile dysfunction • Ischemic priapism • Nonischemic priapism • Recurrent priapism • Urology

Introduction

Priapism is defined as a persistent erection of the penis not accompanied by sexual desire or stimulation, usually lasting more than 6 h and typically involving only the corpora cavernosa and resulting in dorsal penile erection with the ventral penis and glans being flaccid¹. Rare exceptions with involvement of the corpus spongiosum and sparing of the cavernosal spaces have been reported². In some cases, this condition can be an urological emergency and has many different causes. The recently published American Urological Association Guideline on the management of priapism sheds further light on the management of this potentially emergent condition, but the guideline does not establish a fixed set of rules or define the legal standard of care for the treatment of priapism³.

Incidence in a population-based, retrospective cohort study was found to be 1.5 per 100,000 person-years and 2,9 per 100,000 person-years for men aged 40 years and older⁴. For men using intracorporal injec-

Corresponding author:

Giovanni Liguori, Department of Urology, University of Trieste, Strada di Fiume 447, 34144 Trieste, Italy – Tel. +39 0403994096 – Fax +39 0403994895 – E-mail: gioliguori@libero.it

tions to treat erectile dysfunction, the incidence ranges from 1% for the patients who receive prostaglandin E1 to 17% for patients who receive papaverine⁵. In children with sickle cell anemia (SCA), the incidence is reported to range from 6-27%^{6,7}. In adults, the incidence increases up to 42%⁸. A different study in this population reports 89% of males with SCA will have an episode of priapism by age 20. The mean period is 125 min per event⁹.

Methods

Evidence Acquisition

In broad terms, priapism may be regarded as an imbalance between arterial inflow and outflow. Burnett has recently reviewed the pathophysiology of priapism and suggested derangements in the diverse systems of regulatory control in erectile function. These deregulatory functions include possible overactivity of the veno-occlusive mechanism, arterial inflow, or neurogenic processes that can affect inflow or outflow. Conversely, the problem may be secondary to malfunction of the normal contractile activities of cavernosal smooth muscle cells¹⁰.

The aetiology of priapism has been traditionally divided into primary or idiopathic and secondary to some other condition or disease process. In accordance with Pryor, for the purposes of clinical management, it is appropriate to distinguish between high-flow, low-flow and recurrent or stuttering priapism¹¹.

In this paper we aim to provide insight into the pathogenesis and treatment modalities of priapism.

Low-flow priapism

Low-flow, ischemic or anoxic priapism is the most common. The spectrum of clinical symptoms and signs is analogous to those found in other compartment syndromes. It is a prolongation of a normal painful erection and in the idiopathic form is frequently present on walking. During erection there is a relaxation of the smooth muscle in the cavernous arteries and tissue, this is associated with the increased arterial inflow and the decreased outflow of blood. The intracorporeal pressure may rise above mean arterial pressure and the inflow of blood then ceases. The persistence of erection and failure of detumescence, the persistent relaxation and failure of contraction of cavernous smooth muscle is associated with increasing anoxia, a rising pCO₂ and acidosis¹². The prolonged erection becomes painful after a variable length of time; therefore patients are

warned to seek urgent medical attention for an erection lasting more than 4 hours. Early relief is associated with return of normal flaccidity, but more prolonged ischemia is associated with tissue oedema. Histological studies have shown a defined pattern of pathology¹³. Interstitial oedema and thickening are present up to 12 h, by 24 h endothelial thrombocytic adherence is present and by 48 h necrosis of cavernosal smooth muscle cells and fibroblast proliferation has occurred, which may result in subsequent fibrosis and calcification.

In organ-bath preparations using isolated rabbit corpus cavernosum, Broderick et al.¹⁴ data suggest that corporeal smooth muscle tone, spontaneous contractile activity and the response to α -agonists depends on the state of corporal oxygenation. These observations might be an explanation for the failure of locally administered α -antagonists to relieve ischemic priapism because of smooth muscle paralysis. Daley et al¹⁵ documented a significant reduction in prostacyclin (PGI-2) production during hypoxia in rabbit corpus cavernosal cells, which was attributed to inhibition of the enzyme PG-2 synthase. In view of the role of PGI-2 as an inhibitor of platelet aggregation and white cell adhesion, these studies may provide some insight into the changes in corporeal haemostasis during ischemic priapism. Further studies have shown that re-oxygenation of these hypoxic rabbit cavernosal cells generates oxidative stress that interferes with the recovery of prostanoid production¹⁶.

The production of nitric oxide (NO) in the corpus cavernosum is altered by hypoxia because NO synthase activity is affected by changes in oxygen tension¹⁷. During veno-occlusive ischaemic priapism, the entrapped pool of blood that is initially at arterial oxygenation becomes progressively hypoxic. The combined reduction of PGI-2 and NO expected under hypoxic conditions would favour platelet aggregation and white cell adhesion, leading to thrombus formation and tissue damage.

The end result of muscle necrosis after priapism is fibrosis which may be patchy in distribution and it is thought that TGF-beta has an important role in this process

Nieminen and Tammala found that in 21% the cause of priapism was the intracavernosal injection of a vasoactive agent that is injected¹⁸. Papaverine has been associated with a 5% risk at initial diagnostic testing, but a much lower risk when used as therapy¹⁹; most of these cases were in patients with psychogenic or neurogenic impotence.

Pohl et al. evaluated various etiologies for priapism in a study of 230 single case reports in the literature:

idiopathic causes comprised one-third of the cases, whereas 21% were attributed to alcohol abuse or medications²⁰.

The incidence range of priapism episodes is from 1% for those on PGE1²¹. The most likely cause of prolonged erection, as a result of intracavernosal injection therapy, is overdose.

Sildenafil is an orally active agent for the treatment of ED and in well-controlled trials the incidence of priapism appears extremely low, although it has been anecdotally reported in post-marketing surveillance studies.

Drug-induced priapism has been reported with a variety of medications, most commonly related to the antihypertensive drugs guanethidine, prazosin, hydralazine and the anticoagulants, including intravenous heparin, and the oral coumarins²². Generally priapism occurred after cessation of anticoagulant therapy, thus resulting in a rebound hypercoagulable state. Priapism has been reported with a variety of centrally acting drugs including the phenothiazines, paroxetine, fluoxetine and trazodone and cocaine may have synergistic effects in promoting priapism^{23,24}. Cocaine-induced priapism has been reported in association with topical application to enhance sexual performance and intranasal and intracavernous injections. Priapism has also been reported in association with the recreational drug ecstasy²⁵.

Examples of neurologic etiologic factors include priapism in patients with degenerative stenosis of the lumbar canal, priapism secondary to cauda equine syndrome and herniated disk²⁶.

Trauma to the perineum, penis or groin, whilst usually resulting in high-flow priapism, can result in venous compression secondary to penile haematoma or oedema.

Different solid tumors have been associated with priapism, including both bladder and prostate cancer²⁷. Malignant priapism has been reported as the initial presentation of metastatic renal cell cancer, gastrointestinal tract and rarely from testis, lung, liver, bone and sarcoma as a result of invasion of both the corpora and spongiosum. Malignant infiltration may obstruct venous drainage^{28,29}.

Idiopathic segmental thrombosis of the corpus cavernosum, total parenteral nutrition, appendicitis, amyloid and rabies have all been reported as a cause of priapism^{30,31}.

High-flow priapism

High-flow priapism is less common than low-flow priapism and can be classified as congenital due to

arterial malformations; traumatic usually associated with penile, perineal or pelvic trauma, iatrogenic from post revascularization procedures directly to the tunica or idiopathic. The local blood gas tension in these patients is arterial and therefore the penis is not at risk of ischemia and subsequent fibrosis.

The onset of a post-traumatic, high-flow priapism may occur up to 72 hours after the injury. Pain is never as severe as in an ischemic priapism: the penis is often not maximally rigid and pulsation may be visible in the penis.

A mechanism for the pathophysiology of high-flow priapism is described by Goldstein's group in Boston: unlike a traditional arterovenous fistula, the condition is described as an arterial-lacunar fistula where the helicine arteries are bypassed and the blood passes directly into the lacunar spaces. The high-flow in the lacunar space creates shear stress in adjacent areas, leading to increased nitric oxide release, activation of the cGMP pathway and smooth muscle relaxation and trabecular dilatation. These authors also postulate that the delay in onset of high-flow priapism may be secondary to a delay in the complete necrosis of the arterial wall after the initial trauma or secondary to clot formation at the site of injury followed by the normal lytic pathway, which follow in a few days³².

A rare case of high-flow priapism is Fabry's disease, which may be caused by an unregulated high arterial inflow³³.

Recurrent priapism

Recurrent or stuttering priapism is associated with the hyper-viscosity syndrome, the commonest of which is sickle-cell disease which still ranks as the most frequent cause of priapism in children³⁴. In a boy with sickle cell disease the incidence of priapism is of 18-27%³⁵. This poorly understood condition is uncommon and not confined to men with sickle cell disease. The erection is usually during sleep and detumescence does not occur upon waking. These erections usually do not become painful for about an hour. Serjant et al. described "stuttering" nocturnal attacks in 42% of Jamaican adults with homozygous sickle-cell disease.

Recurrent episodes may result in a markedly enlarged penis with fibrotic corpora, which may later lead to ED.

Other haemoglobinopathies, including the rare unstable haemoglobin Hb Olmsted and thrombophilia erythropoietin therapy, the leukaemias and myeloma have also been associated with priapism³⁶.

Discussion

Diagnosis of priapism

A thorough history and physical examination are prerequisites to diagnostic accuracy. The fundamental aim of the initial phase of assessment is to distinguish arterial from ischemic priapism. The sexual and medical history should especially focus on medications, trauma and predisposing comorbidities. Presence or absence of pain is a fairly reliable predictor of low-flow versus high-flow priapism, respectively. Absence of pain in arterial priapism frequently results in less patient anxiety and discomfort as compared with veno-occlusive priapism. Consequently, those with arterial priapism may present days or even weeks after the original injury³⁷.

Physical examination of the penis is critical and typically reveals firm corpora cavernosa and a soft glans, indicating sparing of the corpus spongiosum in low-flow priapism. Findings in high-flow states usually reveal a partial to full erection and sparing of the corpus spongiosum in most cases³⁸.

General diagnostic tests include urine toxicology screening for psychoactive drugs and metabolites of cocaine. It has additionally suggested reticulocyte count; urinalysis; complete blood count; platelets and differential white blood cell count.

Urologic management of priapism requires assessment of corporal blood flow status with corporal aspirate, visual inspection by color and consistency or corporal blood, and blood gas analysis including pH, pO₂, and pCO₂.

Low-flow priapism is suggested by finding low oxygen tension, high carbon dioxide and low pH in the blood gas analysis of the aspirate³⁹. When

a high-flow state is suspected based on the bright red appearance or blood gas analysis of the corporal aspirate, colour Doppler ultrasound is indicated to identify the arterial sinusoidal fistula (Fig. 1). For high-flow priapism, angiography is useful to identify a local bleeding site (Fig. 2).

Blood gas measurements of pH can give an indication of the urgency based on the degree of acidosis. A pH less than 7.10 reflects more aggressive management options and should be sought quickly in that the tissue is a risk for necrosis.

Penile colour Doppler ultrasound is not invasive, does not expose the patient to ionizing radiation and can reveal important information regarding the location of arterial injury in high-flow priapism by recording the turbulent flow that permeates the erectile tissue. Vascular lacuna is evident during selective pelvic angiography when the contrast medium, injected through the pudendal artery, spread the cavernous body and has the radiologic appearance of an arterial fistula⁴⁰. The colour Doppler ultrasound is sensitive as angiography for the diagnosis of high-flow priapism. More specifically, penile colour Doppler ultrasound had a sensitivity of 100% and specificity of 73% with a predictive value of 81% for a positive test and 100% for a negative test⁴¹.

Treatment of priapism

Therapeutic options for low-flow and high-flow priapism are essentially different, reflecting profound differences in etiology and pathophysiology. While ischemic priapism is a urological emergency that must be

Figure 1. In this patient spectral analysis shows the typical waveform pattern of an arteriosinusoidal fistula.

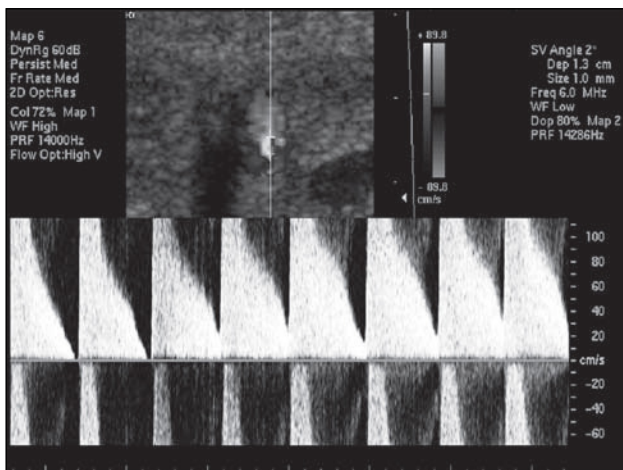
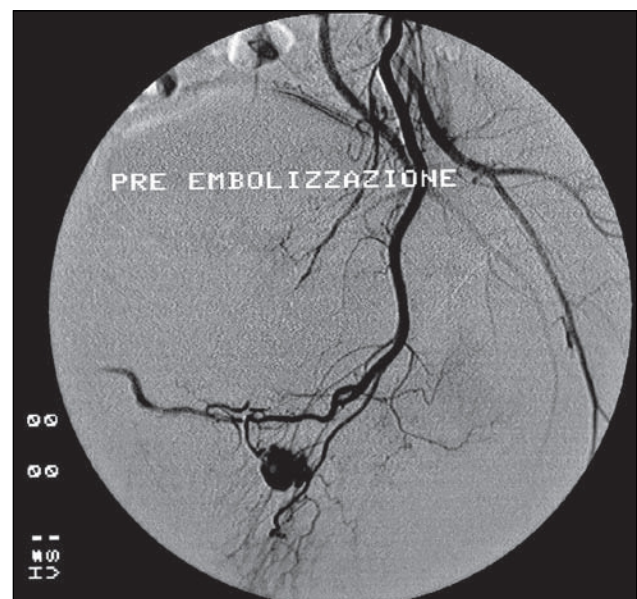


Figure 2. Arterious laceration with a cavity within the cavernosal tissue.



treated immediately, also using invasive procedures, patients with high-flow states are in general at low risk of developing irreversible erectile dysfunction and can be managed more conservatively.

Treatment of low-flow priapism

Therapy of low-flow priapism is based on the underlying cause and will typically follow a pattern of least invasive to more invasive procedures.

Any primary factors involved in the cause of the priapism should be addressed and treated. Pain and anxiety also require therapy, which includes use of parenteral opioids and an anxiolytic if indicated. Ice and elevation are also components of the initial conservative therapy. A penile dorsal nerve block utilizing local anesthesia, circumferential penile block, subcutaneous local penile shaft block and oral conscious sedation for pediatric patient may be of benefit to control pain⁴².

For patients with low-flow priapism of relatively moderate duration (approximately 4 hours) penile aspiration and irrigation with saline remain standard first line management strategies.

For patients with extremely prolonged low-flow priapism, oral terbutaline, an oral β -adrenoreceptor agonist, in a dose of 5-10 mg has been advocated as a treatment with a response rate to 36% of treated patients who had prostaglandin induced priapism as well as therapy for other causes⁴³. Terbutaline also can be given subcutaneously in doses of 0.25-0.5 mg and can be repeated in 15-20 min. Oral pseudoephedrine, α -adrenoreceptor agonist, 60-120 mg orally has been suggested and used as therapy for priapism due to intracavernosal injected agents, but efficacy is not well studied. Treatment with injections into the corpus cavernosum of alpha adrenergic receptor agonists after aspiration would be the next therapy after terbutaline. Phenylephrine, 10 cc, which corresponds to a dose of 200 μ g, is injected into the penis after aspiration. Frequent blood pressure measurements and preferably ECG monitoring are required throughout and failure to respond may require a second injection of 200 μ g and a final dose of 500 μ g. Alternatively, epinephrine can be injected in 1-3 cc boluses up to 10 cc⁴⁴. Methylene blue has been shown to be useful as an alternative to alpha agonists, with a mechanism felt to be related to inhibition of cyclic GMP, which in turn inhibits smooth muscle relaxation⁴⁵. Intracavernosal injection with 50 mg of methylene blue followed by aspiration and penile compression for 5 minutes. Transient penile burning and blue discoloration lasting for about 3 days were the reported side effects⁴⁶.

If these relatively simple measures fail, surgical intervention is required. A variety of techniques has been described, including The Winter procedure using a Trucut needle (Fig. 3) and the Ebbehøj using a pointed scalpel blade to create a shunt between the glans and corpora cavernosa. El-Ghorab technique is a more invasive procedure that involves excision of a small disk of tunica albuginea. These techniques fail in about a third of patients.

Use of intracavernosal thrombolytic medications, including tissue plasminogen activator, has been recently described, although the efficacy is uncertain and long-term prognosis are lacking⁴⁷.

In a man with a late presentation of a low-flow priapism – more than 72 hours – consideration should be given to the implantation of a penile prosthesis.

The treatment of sickle cell priapism requires more disease-specific treatment, including oxygenation, hydration, alkalinization, exercise, analgesia and exchange transfusion. Anecdotal evidence supports the use of oral therapy with hydroxyurea and hydralazine⁴⁸. Etilefrine is an oral α -adrenoreceptor agonist that in the form of maintenance therapy may help prevent further attacks, with little effect on systemic blood pressure⁴⁹.

Surgical spinal decompression has been recommended to alleviate priapism associated with lumbar spinal stenosis.

Treatment of High-Flow Priapism

The clinical history and initial investigation, coupled with selective angiography, should confirm the diagnosis of high-flow priapism. The initial treatment should be observation. This approach is based on the

Figure 3. Winter procedure using a Trucut.

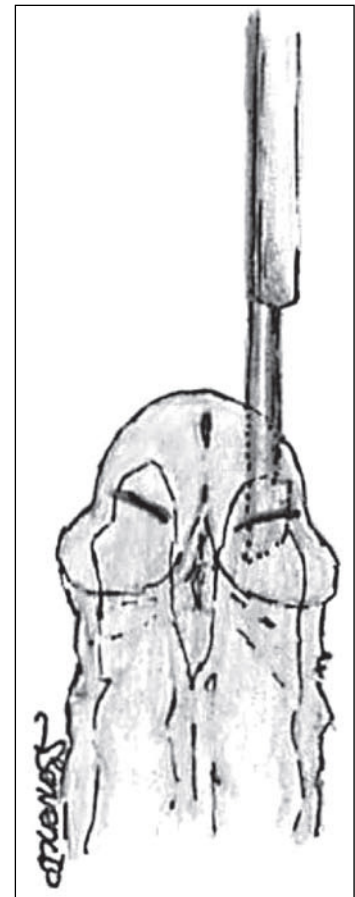
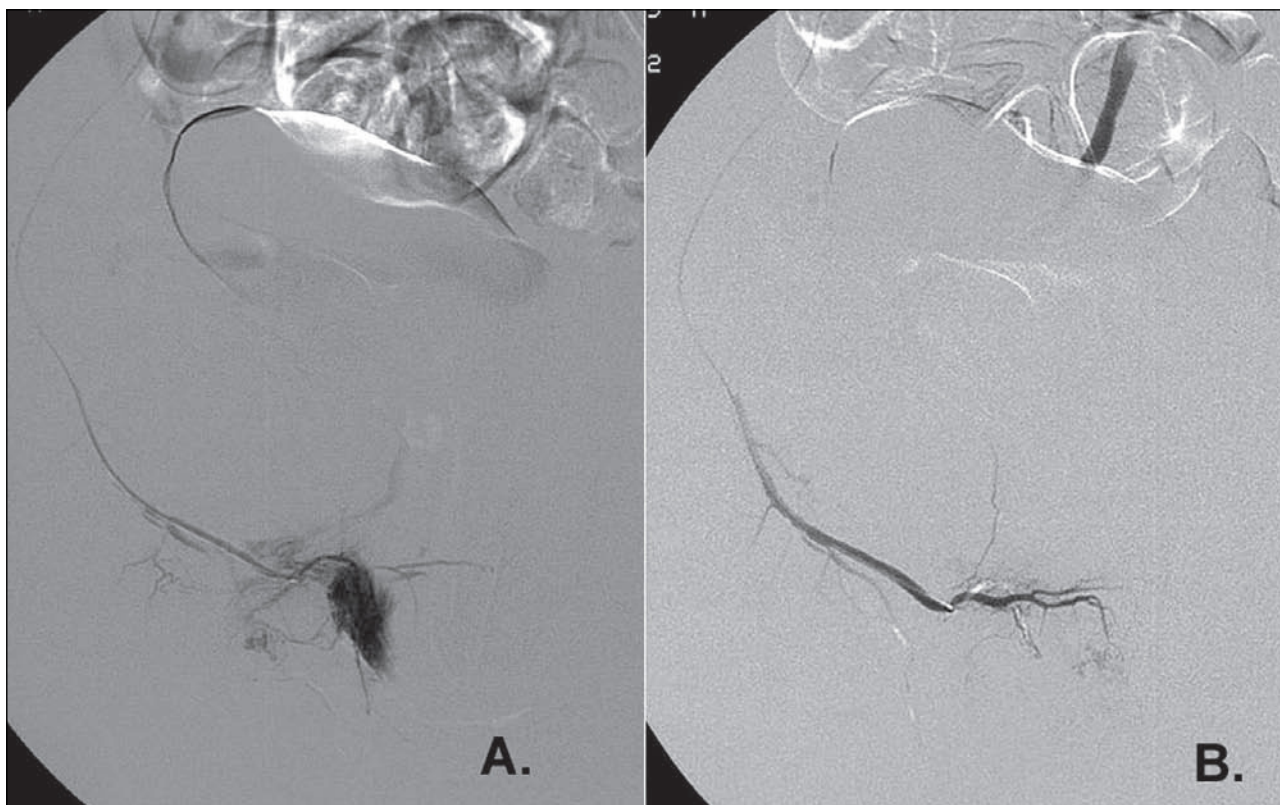


Figure 4. a) Pre-embolization location of the arterial-lacunar fistula. b) Absence of flow after the embolization with absorbable materials.



finding that expectant management results in spontaneous resolution in 62% of the report cases. The others cases are best managed by an interventional radiological procedure to embolize the responsible vessels using either autologous blood clot, silver coils, Geof foam polyvinyl alcohol or N-butylcyanoacrylate although several attempts may be necessary (Fig. 4). Open surgical ligation of the responsible vessels using intraoperative ultrasonographic guidance may be used when conservative and minimally invasive methods have failed.

Complications

Early complications typically result from injection of α -adrenergic agents and include headaches, palpitation, hypertension and cardiac arrhythmias. Vital signs should be monitored during this phase of therapy. Additional adverse events include urethral injury and urethrocutaneous or urethrocavernosal fistula from aggressive needle decompression, bleeding and infection⁵⁰. Rare cases of gangrene of the penis after corporospongiosal shunt have been reported.

Prognosis

Impotence rates from 35-60% have been reported when priapism persist for 5-10 days, respectively.

When the priapism has been ongoing for over 24 h, treatment with aspiration alone is often unsuccessful and will usually require irrigation and often injection. Treatment should be initiated within 12 h of the onset of symptoms to avoid long-term dysfunction and irreversible infarction, with the corollary being the earlier the resolution of symptoms, the better the long-term prognosis.

Conclusion

Current management strategies suffer from a poor understanding of the pathophysiology, especially at the molecular level. The traditional treatments are based more on empirical rather than evidence-based knowledge. Therefore, it is critical to understand priapism from a molecular level, to formulate treatment strategies and to establish rational prevention strategies. When the physician first diagnoses which type of priapism exists, distinguishing the type of priapic event is paramount in order to choose the correct treatment options. Until recently, we had not sufficiently understood the pathogenesis of this erectile disorder and therefore, could not effectively manage its pathologic consequences of erectile tissue damage and erectile dysfunction.

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