Chapter

Erectile Dysfunction Caused by Cavernous Leakage

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Abstract

Erectile dysfunction (ED) is a big issue in various populations with up to 30% of young men suffering from this condition. Unfortunately, treatment schemes are currently mainly focused on elderly patients with chronic disorders. In younger patients, ED is more a vascular problem, which affects the storage capacity of the penis. The impact of penile blood supply on erectile function was recognized some 500 years ago. At the turn of the twentieth century, the first results of penile venous ligation were published. Simple isolated ligation of the deep dorsal vein in humans for ED due to venous leak is currently not recommended, due to some reported low long-term success rates. This was, as shown in several literature reports, obviously due to insufficient technical possibilities. Technical development in imaging and vascular and endovascular treatment have dramatically evolved our understanding of this underlying condition in the past 20 years and turned this disease into a long-term treatable condition. The current state-of-the-art work-up of the underlying condition, using the newest imaging technologies with color Doppler ultrasound and CT scan with additional three-dimensional reconstruction, is to show the surgeon exactly the points to focus on. Additionally, a so-called corporo-venous insufficiency can be recognized as a mainly combined condition, affecting peripheral and more proximal drainage pathways at the same time.

Keywords: erectile dysfunction, venous leak, venous leak diagnostic, venous leak treatment, CT cavernosography

1. Introduction

Erectile dysfunction (ED) is a big issue in various populations with up to 30% of young men suffering from this condition with an increasing tendency.

Cavernovenous leakage is a venous insufficiency located at the penis in which blood fails to accumulate in the corpora cavernosa because of pathological drainage of blood from the penis due to an abnormal or insufficient venous network [1, 2].

Consequently, pressure in the corpora cavernosa does not rise properly, and the resulting erection is insufficient to achieve or maintain intromission during sexual intercourse.

Furthermore, ED commonly affects the physical, psychological, and social health both of patients and their families, which can have an overall detrimental effect on the quality of life [3–5].

Papaverine intracavernosal injections (ICIs) [6] and oral medications were introduced 21 years ago [7] and have revolutionized the medical treatment of ED. Unfortunately, treatment schemes are currently mainly focused on dealing with relevant chronic disorders in elderly patients. Overall, oral treatments with PDE5 inhibitors (e.g., sildenafil (Viagra), vardenafil (Levitra), tardalafil (Cialis), and avenafil (Spedra)) are ineffective in about 30% of patients with ED [8, 9]. Despite a drug-induced increase in inflow, cavernovenous leakage is responsible for the failure to retain the blood in the penis in half of these cases [10, 11].

Up to 86% of patients resistant to intracavernous drug injection with papaverine or prostaglandin E1 have a cavernovenous leakage [12, 13].

A cavernovenous leakage is also responsible for half of the cases of severe ED, which affects 1–4% of men under the age of 25 years [14, 15].

Despite its high prevalence, cavernovenous leakage usually remains undiagnosed. Consequently, young patients with drug-resistant ED refusing a penile implant are unable to achieve sufficient and satisfying sexual intercourse.

Contrary to the long-held belief that erectile dysfunction due to venous leak is a purely human problem, there are many descriptions of this condition in different species like bulls, boars, dogs, and monkeys [16–20].

2. Pathophysiology

The etiology of venogenic erectile dysfunction is not exactly known.

Various pathologic processes were accused but none proved entirely satisfactory.

The in-flowing blood through arteries into the penis is stored in the erectile tissue, and this leads to an increase of pressure in the penis and an increase of length and hardness of the penis.

Known possible causes of the venous leak are congenital vascular anomalies, arterial insufficiency, trauma and post-priapism, diabetes, and Peyronie's disease [21].

Notwithstanding this, there are a plethora of other causes, and the exact epidemiology is not fully understood up to now.

Venous insufficiency in principle [22] can result from

1. structural changes in the vein wall (hereditary) [23],

2. venous hypertension (e.g., Peyronie's disease),

3. inflammation (e.g., diabetes),

4. alterations in shear stress, and

5. improper closure of emissary veins.

A leak will result in the outflow of blood from the penis and an insufficient erection.

1. Hereditary and acquired conditions inside the tunica albuginea or outside the cavernous corpus itself can lead to a clinically significant venous leak.

2. Cavernosal smooth muscle damage results in insufficient sinusoidal relaxation and expansion during tumescence, leading to improper closure of emissary veins as the albuginea layers are inadequately compressed.

The majority of venous leak conditions are either located outside the corpus cavernous or inside the tunica albuginea (e.g., Peyronie's disease) itself and cause a more physical problem. Therefore, the underlying physical mechanisms are further discussed in the next chapters.

The tunica albuginea of the corpora cavernosa has a bi-layered structure with multiple sublayers. The inner layer bundles are oriented circularly and support the cavernous tissue [24].

The radiating columns emanating intracavernously from this layer act like struts, enlarging the septum and providing substantial support to the erectile tissue. The outer layer bundles are oriented longitudinally. These fibers extend from the tip of the corpus cavernosum to the proximal crura, where they enter the inferior pubic ramus [24].

On a cellular level, the intracorporal pressure of patients with cavernovenous leakage is significantly lower than in healthy controls with resultant atrophy to the tunica albuginea. This in turn is resulting in a failure of compression both of the subtunical venular plexus and the emissary veins, consequently leading to a venous leak [25].

Therefore, patients' veno-occlusive dysfunction can also or additionally result from endothelial dysfunction and damage to the trabecular smooth muscle content because of ongoing multifactorial degenerative processes [21].

If any hereditary or acquired condition can lead or add to these degenerative processes of cavernous tissue, then it cannot be answered up to now.

3. Physical principles

Irrespective of many assumptions, some of which are mystical, the processes in the penis, similar to hydraulics, are also subject to the physical laws of hydrostatics and hydrodynamics.

The use of cadavers, which eliminated the influence of hormonal, arterial, neurological, sinusoidal, pharmacological, and psychological factors, demonstrates that the human erection is fundamentally a mechanical event contingent on venous competence [26].

In principle, the development of an erection can be divided into two phases:

1. Filling phase:

   A. Filling of the body of the penis via the inlet (arteries).

   B. Reduction—blocking the outlet (veins). The pressure in the cavernous corpus can reach the blood pressure (130 mmHg to 150 mmHg) at most.

2. Stiffening phase

A. Compression of the cavernous corpus on the part of the body that is surrounded by muscles (pelvic floor muscles). This increases the pressure in the penis up to 10–40 times the blood pressure to achieve a full erection. Due to the compression, the pressure propagates evenly in all directions.

B. In the event of a disturbance in the pressure on the lateral surface of the penis, there is a drop in pressure in the penis and, thus, changes in shape that affect the firmness of the penis.

Blood as a liquid shows no resistance to changes in shape but great resistance to changes in volume and is, therefore, subject to the criteria of an incompressible medium.

According to the principles of hydrostatic pressure by Pascal, this propagates evenly in all directions.

If a flowing liquid (blood) does not change its volume, the same volume of liquid must flow through the different cross sections of the line (artery, penis, and vein) every second. According to the Bernoulli equation, the sum of the pressure level, the velocity level, and the local level is constant over the entire length of the line (artery, penis, and vein). This means that the total pressure of the liquid is the same at every point.

With a "simple" blockage of the venous outflow, the pressure in the penis increases to the maximum of the blood pressure. In practice, this leads to the state of full tumescence.

Any further increase in pressure can only be achieved by either an active additional blood supply through pumping or by compressing the body from the outside (pelvic floor muscles, mainly the ischiocavernosus muscles at the penile base).

These fundamental principles can be represented in a (simplified) model for further mathematical-physical calculations (see **Figure 1**).

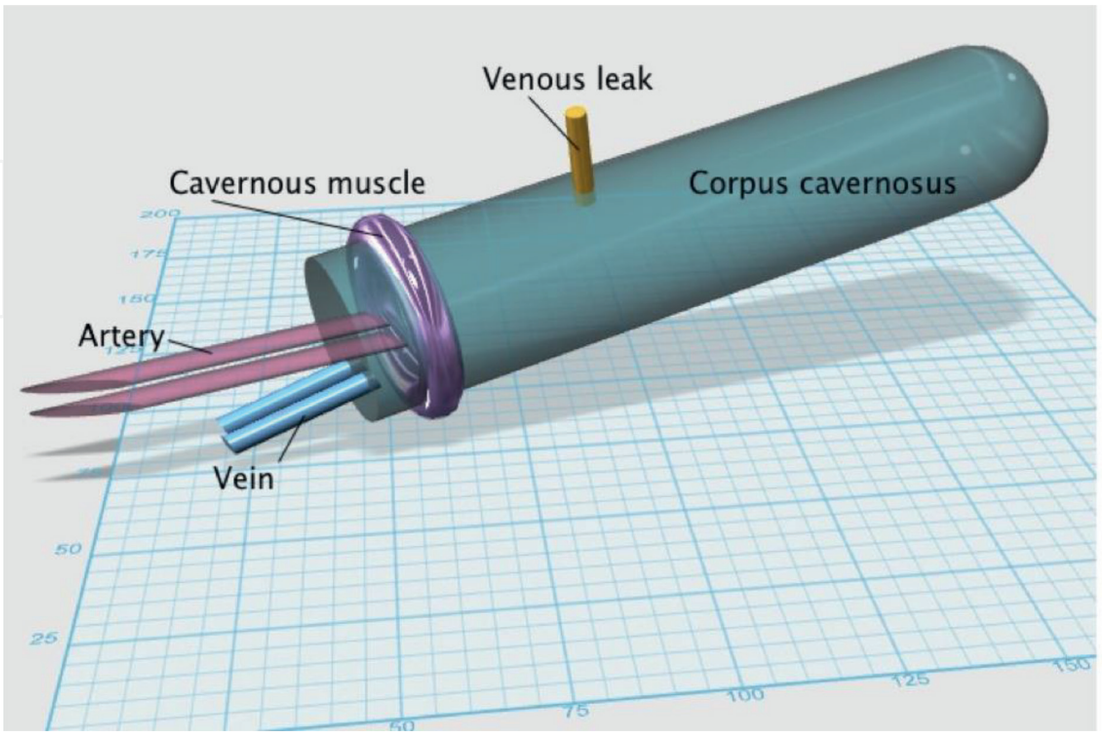


Figure 1.
Physical model of the penis.

Starting from the hydrostatics to the hydrodynamics and firmness of the penis, simple mathematical methods (finite elements) result in the spatial representation of the force and tension distributions on the surface and inside the penis. Using the physical model and the examples presented, the effluent time of the blood from the penis can be determined as a function of the total diameter of the venous leak [27].

Furthermore, prognoses can be a priori calculated in a specific patient example, which enable the surgeon to decide whether and to what extent deficiencies are likely, which are more likely to be addressed with medication or might require surgical treatment.

Application of this model demonstrates that an overall venous leak diameter of 1.5–2 mm is sufficient to induce penile de-tumescence within 30–50 s. This calculation corresponds exactly to the clinical picture (**Figure 4**).

4. Clinical presentation

Patients with congenital significant moderate-to-severe venous leak mostly report a lifelong inability to achieve a full erection under any circumstance and typically are in a younger age group [28, 29].

They usually describe erection as insufficient for intercourse or of only a short duration. Early-morning and nocturnal erections are also described as weak or absent, whereas libido is communicated as normal.

Typical complaints also include a constant soft erection barely enough for sexual intercourse, position-dependent penile rigidity, difficulty in achieving an erection, and difficulty in maintaining erections without manual stimulation. Also, a loss of penile length and girth over time and a soft glans of the penis during erection (also known as cold/floppy glans syndrome) [30, 31] are sometimes described.

Acquired cavernovenous leakage presents more or less in the same way but is preceded by a traumatic episode, for example, a road traffic accident, during sexual intercourse, or after radical prostatectomy. The patient usually offers a history of normal sexual function prior to the index accident. Not uncommonly, there may be low sexual desire secondary to the accompanying psychological burden [28].

Examination to rule out other causes of libido loss (e.g., hypogonadism) is only useful if the patient does not have normal secondary sexual characteristics, normal genitalia, or good peripheral pulses.

If a patient describes one or more of the symptoms listed above, physicians should be alert and, particularly in young patients, should look for signs that suggest an organic rather than a psychological cause of erectile dysfunction.

Such suggestive signs include

- Erectile Dysfunction persistent on all occasions where an erection is required, including with a partner or during masturbation.
- Loss of quality of morning erections.
- Loss of quality of spontaneous erections.
- Multi-treatment resistance to traditional erectile dysfunction medications including PDE5 inhibitors and ICI.

5. Diagnostic

5.1 Color Doppler Ultrasound

Dynamic color duplex Doppler ultrasound (CDDU) of the penis, first described by Lue et al. [32], is an objective and reliable diagnostic method for documenting penile hemodynamics.

Color Doppler evaluation of erectile dysfunction has also been shown to be an effective method for differentiating psychogenic and vasculogenic causes of erectile dysfunction [33].

Objective vascular testing that provides a physiologic diagnosis may help to direct the patient to an appropriate therapy.

The reasons for a lack of response to sexual stimulation based solely on medical history and standardized questionnaires (e.g., International Index of Erectile Function [IIEF] [34]) can be misleading.

Penile CDDU is required to complete evaluation in young males with primary or secondary ED and/or a history of pelvic trauma, substance abuse, prior to surgical procedures to treat Peyronie's disease. A distinction can be made between psychogenic and organic, particularly in the presence of a venous leak and in forensic cases.

The CDDU is first performed in a relaxed state, scanning the entire penis (in B-mode image) using a 7.5–12-MHz linear array ultrasound probe. This is followed by an intracorporal injection using a single or combination of vasoactive agents (e.g., prostaglandin E1, phentolamine, and papaverine), and CDDU is performed at various time points [33].

Criteria for diagnosing a venous leak are differing in various publications.

It is commonly agreed that a peak systolic blood flow (PSV) > 30 cm/s, an end-diastolic velocity (EDV) of < 3 cm/s, and a resistance index > 0.8 are generally considered normal.

A PSV below 25 cm/s is diagnostic of arterial insufficiency as the cause of ED [33, 35].

The EDV and the corresponding calculation of the resistive index (RI) are informative about penile veno-occlusion. Venogenic ED (corporo-venocclusive dysfunction or venous leak) is deemed present when the EDV and the resulting RI are abnormal with a normal PSV. Mixed vascular insufficiency is diagnosed when both PSV and EDV values were abnormal.

Using the evaluation of PSV, EDV, and RI measurements, the peak tumescence, and rigidity response, based upon the clinical history, the patient's penile vascular status can be classified as nonvascular, partial arterial, arterial, partial venous, venous, borderline mixed, or mixed as detailed in **Table 1**.

Furthermore, it is postulated that proper diagnosis of venous leakage should include both color Doppler flow analysis and computed tomography cavernosography for adequate patient selection and treatment planning [36].

5.2 Subtraction angiography and magnetic resonance tomography (MRI)

Either subtraction angiography or high-resolution arterial images similar to digital subtraction angiography with a CT scanner can be obtained [37] to demonstrate arterial inflow deficiencies.

	PSV	EDV	RI
Nonvascular	>30 cm/s	<3 cm/s	>0.8
Partial arterial	Between 25 and 30 cm/s	<3 cm/s	>0.8
Arterial	<25 cm/s	<3 cm/s	>0.8
Partial venous	30 cm/s or above	3–6 cm/s	0.6–0.8
Venous	30 cm/s or above	6 cm/s or above	<0.6
Borderline mixed	Between 25 and 30 cm/s	3–6 cm/s	0.6–0.8
Mixed	<25 cm/s	6 cm/s or above	<0.6

Table 1.
Classification of ED according to CDDU vascular status.

MRI can contribute useful information for many different pathologies in the penis. It is probably useful in investigating a painful penile implant or acute low-flow priapism. Sometimes, it may be useful for local staging of penile cancer, for localization of penile fracture, or for imaging complex cases of fibrosis.

But, in many cases, it is not convincingly superior to clinical examination or ultrasound.

Images of the venous system with an MR angiography may demonstrate the branches of the internal iliac vessels and can be used to plan pelvic revascularization, but are not of adequate resolution to show the penile vessels well, and conventional angiography is superior [38].

In evaluating erectile dysfunction, MR imaging has only limited value and has not yet proved adequately superior to other modalities to justify its routine use [39].

5.3 Three-dimensional (3D) computed tomography (CT) cavernosography

Recent technological developments allow us to reconstruct three-dimensional (3D) images from cross-sectional image data.

CT cavernosography can more accurately describe the anatomical and pathological conditions, either before or after interventions on the vascular system of the penis, than currently used plain X-ray methods. Furthermore, based on this technique, new functional and therapeutical models and principles can be developed to more effectively cure vasculogenic erectile dysfunction.

A penile CDDU only describes the presence or absence, and possibly the hemodynamic extent, of a venous leak. Therefore, this method can only tell us if there is a venous leak, not where the leak is and its complexity.

Especially in case of positive CDDU findings for venous leak, an additional CT cavernosography should be performed to morphologically demonstrate leakage of penile veins. These CT images can especially reformat data using multiplanar reconstruction, maximum intensity projection, and the volume rendering technique is able to depict details of venous leakage. This includes penile veins, the origin of the crural vein, the formation of the periprostatic venous plexus, the pudendal veins, and a pathological drainage into iliac or femoral veins.

According to this technique, penile venous leak drainage can be divided into three groups: superficial veins, intermediate veins, and deep veins [40, 41].

Hence, CT cavernosography not only is beneficial in terms of diagnosing a venous leak but is also useful for patient selection for either surgical or endovascular management.

According to Ye et al., CT cavernosography should be performed after intracavernosal injection of 20 μg prostaglandin E1. Afterward, a 7-G needle is placed into the corpora cavernosum and injection of 30–60 ml of 30% nonionic iodinated contrast medium (320 mg ml^{-1}) diluted with saline is performed using an infusion velocity of 6–180 ml min^{-1} [41]. Scanning range extends from the upper brim of the true pelvis to the most distant level of the penis. The data constructive section thickness is 1 mm with a reconstruction increment of 1 mm for post-processing.

The superior visualization of the complex venous draining system in a 3D-CT cavernosography was first described by Virag and Paul [42] and could be verified by Ye et al. [41], Uhl [43], Herwig et al. [44–46], and Xu et al. [47].

3D-CT cavernosography after ICI is able to differentiate between various venous pathways in men with venous origin ED, leading to this new anatomical classification [42].

In **Figure 2**, the 3D-CT cavernosography demonstrates no venous outflow with a completely competent closing mechanism and can be diagnosed to have no venous leak after prostaglandin E1stimulation with a venous drainage classification A according to Virag et al. [42].

The picture in **Figure 3A** and **B** describes the complexity of venous leakage disease and the need for a more combined renovation of the situation.

This might also explain the fact that neither simple ligation of only penile veins nor ligation of crural veins could deliver good long-term results in the past.

Due to the fact that the related veins are also connected via the deep pelvic vein system, these pictures might reveal the unexplained relation between erectile dysfunction and hemorrhoids [48], as well as possible erectile dysfunction after hemorrhoid sclerotherapy [49].

These pictures with new higher sophisticated techniques also demonstrate the urgent need to reexplore the pelvic and penile veinous drainage system [41].

Therefore, this in many cases underlying combination of cavernosal and crural insufficiency should be addressed in one procedure to prevent early relapse [41, 45, 50].

6. Treatment of venous leak

Currently offered treatment options like PDE5-inhibitor treatment, ICI, testosterone substitution, psychotherapy, pelvic floor training, or penile implant do in many cases not offer a sufficient solution and harbor dangers and complications:

- PDE5 inhibitors may be not sufficient in many cases (see above).
- ICI may be not sufficient and causes tissue damage with prolonged use (see above).
- Testosterone substitution may cause infertility due to dysregulation of the pituitary-gonadal axis.
- Pelvic floor training only might be successful in patients with mild symptoms [51].
- Penile implant offers a mean life expectancy of 5–10 years before replacement or removal is needed [52].

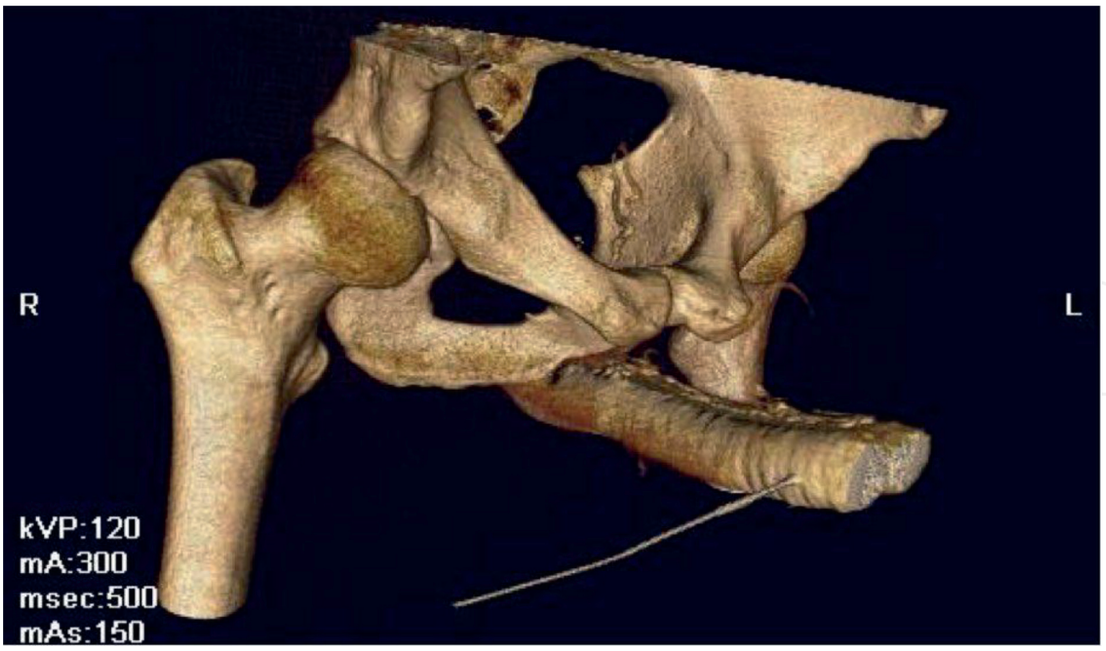


Figure 2.
No venous leak after alprostadil stimulation and venous drainage classification A according to Virag and Paul [42].

In recent studies, these aspects are respected in a newly described technique, which reaches the deep dorsal vein system, as well as the crural venous system [53–55].

The deep dorsal vein is prepared at the proximal penis shaft. A ligation of the vein toward the glans closes the primary leak from the deep dorsal vein. Furthermore, the major penile leakage points, localized by 3D-CT cavernosography, can be closed using distal and proximal ligations. In the second step, a 5F-Angiokatheter is inserted into the proximal part of the vein toward the periprostatic plexus. Under Valsalva maneuver, which must be performed by the patients, the blood flow is reduced or completely stopped in the lower pelvis equal to the compression described in general surgery guidelines for foam sclerosing of various veins.

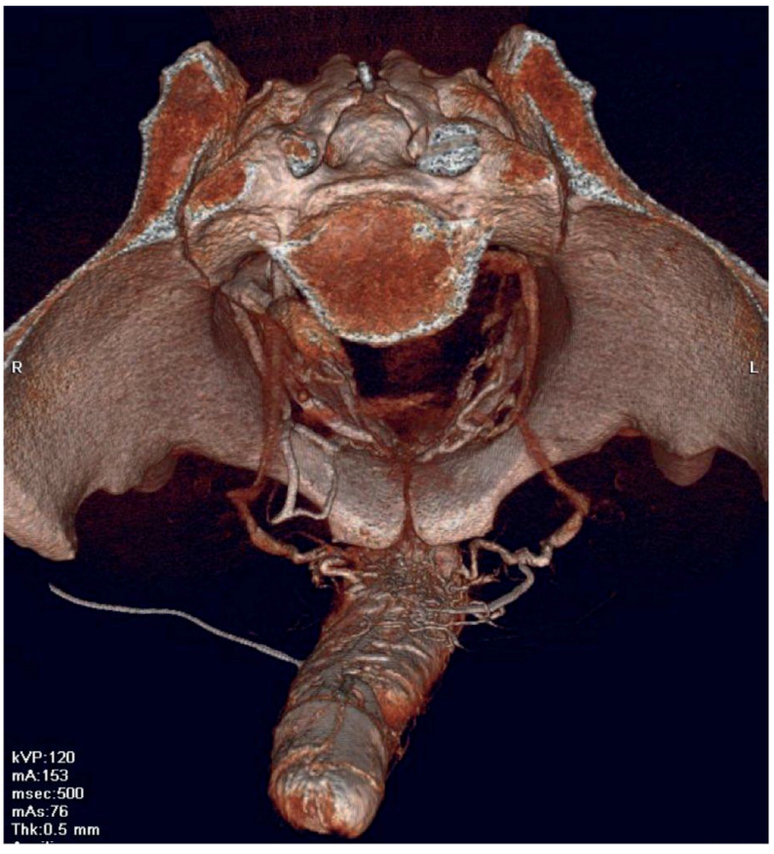
When injecting polidocanol as a sclerosing agent during Valsalva maneuver, the agent can stay longer at the venous wall and the effect of the sclerosing therapy is maximized. In optimal cases, no residual crural or deep dorsal vein leakage can be detected after combined ligation of the deep dorsal vein and antegrade (toward the prostatic plexus) sclerotherapy procedure.

Therefore, this method is providing a therapy for deep dorsal vein and crural venous leakage in a minimal invasive setting at the same time [53–55].

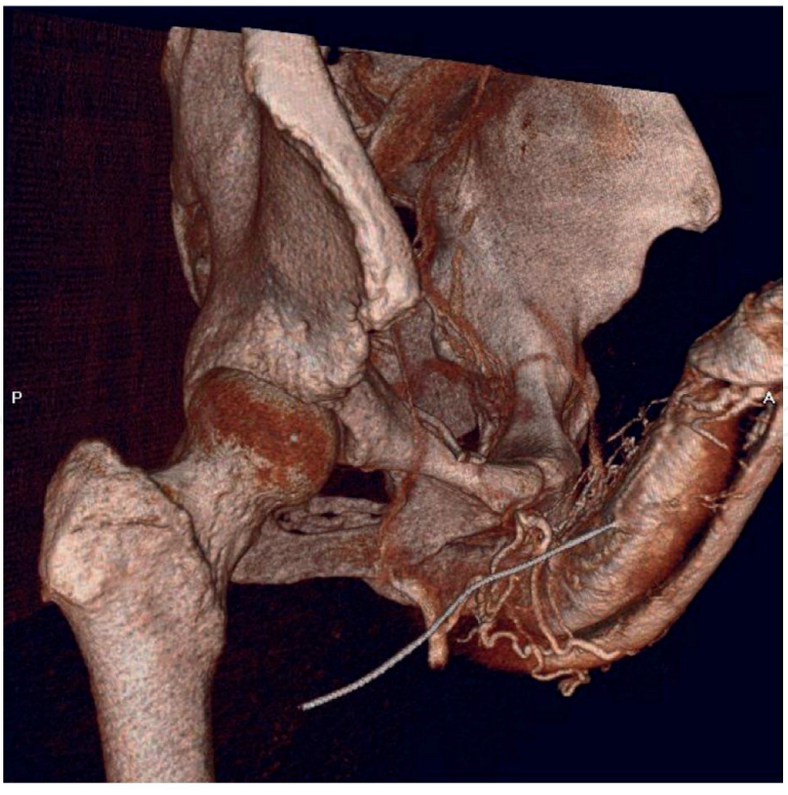
With this newly described technique, at a 3-month follow-up, 77 out of 96 patients (80.21%) reported to have sufficient erections for vaginal insertion without the use of any drug or additional device [55].

These data could be verified by Carrino et al. [53], who recently reported a success rate of over 90% in more than 170 patients treated with this combined technique. Furthermore, the overall cure rate was 77%, which exceeds the effectiveness of PDE5-inhibitor therapy and additionally offers a long-term cure for erectile dysfunction [53].

More recently, Allaire et al. reported a primary success rate of 73.3% and a secondary success rate of 82.2% after a 14-month follow-up, preoperative work-up, embolization, and open surgery during the same procedure. This allowed patients



(a)



(b)

Figure 3.
(A) Venous leak Type D according to Virag and Paul [42] (view into the pelvis) and (B) venous leak Type D according to Virag and Paul [42] (view from the side).

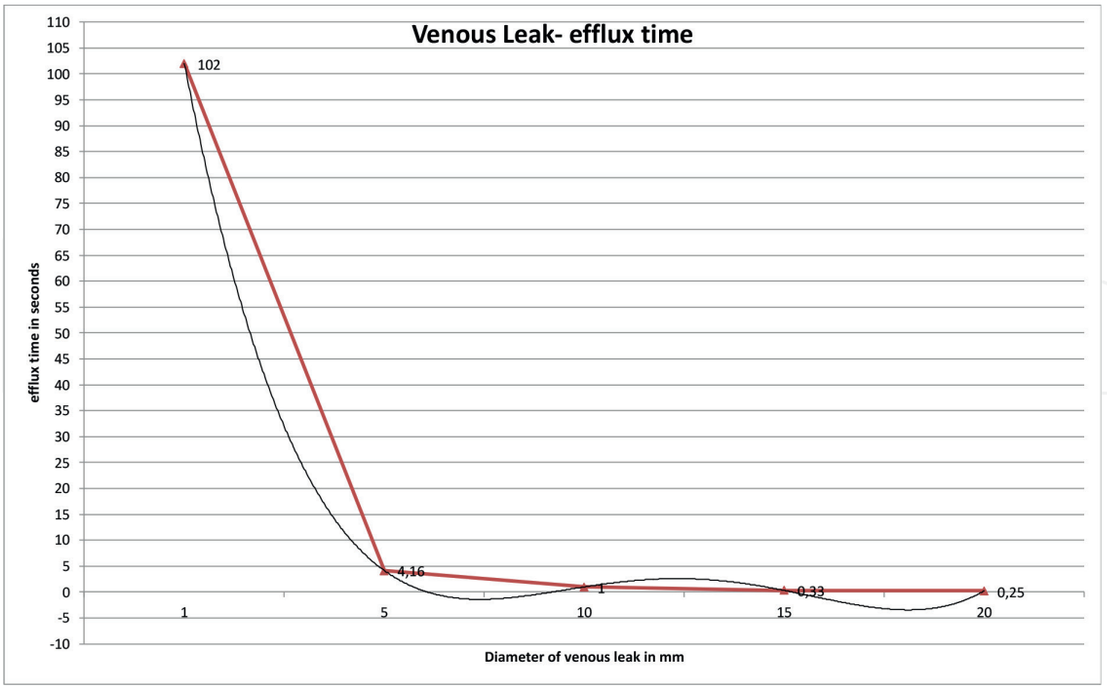


Figure 4.
Blood outflow time according to total diameter of venous leak.

with ED resistant to oral medications to achieve intercourse with normal unaided penetration [50].

In a very recent meta-analysis of almost 540 patients [46], these new and encouraging techniques demonstrated results with a short-term success rate of nearly 80% and long-term success in 73.7% of treated patients.

Regarding the applied method, a slight advantage toward a combination of ligation and antegrade sclerotherapy is found with a short-term success rate of 80% and a long-term success rate of 81.66% in altogether 267 patients [46].

According to these results with these new techniques, Rebonato et al. and Aschanbach et al. [56–58] stated that embolization techniques should be considered in all cases of erectile dysfunction due to venous leak, especially in young patients. Although the technique is not always described to be successful in restoring completely the erectile function, in most cases, the patients regain a satisfactory erectile function with additional use of small amounts of prior ineffective oral pharmacotherapy (PDE5 inhibitors) or delaying the time to penile prosthesis.

These results, although they have to be confirmed by further randomized controlled studies, verified the value of minimal invasive methods in the therapy of erectile dysfunction in patients with venous leakage. The published methods can be carried out under local anesthesia and do not contain major risks or complications [46].

A combined therapy model is possibly needed to support mostly young patients suffering from venous leak caused ED and prevent them at least partially from lifelong continuous medical treatment with all well-known disadvantages and complications.

A systematic review of the literature revealed a significant number of recent studies dealing with new minimally invasive methods that provide a potential solution for venous leakage [46].

The reported long-term results demonstrate significant improvement in ED caused by venous leakage [46].

Over 30 published studies were found in the literature with good results after minimal invasive treatment of cavernovenous leak. Altogether, 13 comparable studies including 538 patients, in which a mean short-term success rate of almost 80% and a mean long-term success rate of up to 74% were achieved (**Table 1**). None of these studies described major complications [46], it is essential to inform the patient about the possible unsuccessful result and perhaps additional treatment with low-dose PDE5 inhibitors to restore over years additionally acquired corporal smooth muscle weakness. Therefore, good patient compliance is essential.

Improvements in techniques, imaging, and sclerosing agents have opened the door for sophisticated minimally invasive venous embolization procedures [59].

Although venous surgery or embolization for the treatment of venous-occlusive disease is in general, according to some guidelines, still not recommended, these procedures can be performed with appropriate informed consent and should follow standardized methods of diagnosis as described above. The work-up before and after surgical treatment should include the use of standardized questionnaires (IIEF) and a long-term (24-month minimum) follow-up [59].

According to Sohn et al., young patients with congenital, post-inflammatory, or post-traumatic leaks may be considered for vein ligation with informed consent. The choice of treatment offered should be decided on available wisdom and infrastructure, the experience and preference of the performer, and be based on the site, nature, and size of the venous leak [60].

Besides simple surgical ligation of penile draining veins, endovascular treatment and combined focused methods may demonstrate more promising results [36].

7. Summary

Veno-occlusive dysfunction resulting in ED is undoubtedly a definite clinical entity but remains under-researched. Unfortunately, a significant number of questions at all stages of the patient pathway are unanswered up to now.

The inability to account for the brought range of degrees of arterial insufficiency and by the potential presence of minor but still significant venous leak sites under-detected in the presence of a greater leak is hindering the investigations. In many cases, the true etiology of the disease remains elusive, since the diagnostic clarification is largely standardized, but reliable reproducibility has not yet been fully achieved.

Offered management options in the past were mainly based on resection or ligation of the venous drainage either at the penis or inside the lower pelvis with a significant decline in efficacy after a follow-up exceeding 12 months, perhaps because of collateral drainage.

It is obvious that venous leakage represents a spectrum of severity. Clinically there seems to be a critical level of dysfunction, in part probably related to arterial inflow and volumetric change of the penis, at which a patient becomes symptomatic. As a result, with higher degrees of arterial insufficiency, a lower degree of veno-occlusive dysfunction would result in ED than would be required in the presence of adequate arterial inflow.

ED is an increasingly important issue, especially in young men. While current treatment strategies focus mainly on older men, young patients are more interested

in a definitive or at least longer-term solution to the problem, rather than lifelong medical treatment. Various chronic disorders have been reported to be associated with elevated rates of ED including depression, diabetes, and cardiovascular and neurological disease in older men. This is mainly not the case in young men. Therefore, properly selected cases of young men may benefit from invasive treatment of cavernovenous leak treatment, and current general treatment strategies in young men should be reconsidered.

A systematic literature review demonstrates possible acceptable short-term and long-term success rates in properly selected cases, justifying a new look at the treatment of cavernovenous leak in young men. Modern techniques such as 3D-CT cavernosography may provide unprecedented opportunities for imaging and surgical planning.

Based on these data, a precise outflow blockage can be performed, not only in peripheral veins but also in deeper pelvic veins. The outcome of this technically advanced procedure is honored with an extraordinary long-term outcome of curing up to 82% of patients without further usage of additional treatment.

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