INVESTIGATION OF ERECTILE DYSFUNCTION

Diagnostic Testing for Vascular Factors in Erectile Dysfunction

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Erectile dysfunction (ED), defined as insufficient rigidity of the penis to penetrate, is broadly classified into two categories: organic and psychologic. In reality, most of the patients demonstrate a combination of organic and psychologic components. Therefore, one should keep in mind that the term vascular ED does not rule out the presence of contributing psychologic factors, but merely means that vascular factors are the predominant cause of ED. Obstruction in the penile inflow tract, denoted as arterial ED, and the inability to trap blood within the cavernous corpora, denoted as veno-occlusive ED, are the two causes of the clinical entity known as vascular ED. In diagnosis of ED, a frequently asked question is "what is the most adequate, goal-directed evaluation in today's cost-conscious environment?" Because current treatments are beneficial for almost all types of ED, one wonders if it is necessary to perform any evaluation at all.

Several tests are available for evaluating the penile vascular inflow and outflow tract, ranging from simple pharmacotesting to enhanced pharmacotesting such as in pharmacopenile duplex ultrasonography (PPDU), cavernosometry, selective penile angiography, and radionuclear imaging. Each method has its pros and cons, related to validity, costs, invasiveness, and availability. The choice of vascular tests should always depend on the purpose of testing: assessing erectile capacity, locating a specific vascular lesion for surgical treatment, or defining the vascular status in groups of patients with a specific disease.

A practical purpose for diagnostic testing may be assessment of erectile capacity: Are arterial response and veno-occlusion, together resulting in erectile response, sufficient for nonsurgical treatment of ED, such as auto-injection therapy? Or is implantation of a penile prosthesis necessary? An adequate test for this purpose is the pharmacotest in the office, or eventually a trial of auto-injection therapy at home. One should realize, however, that an adequate erectile response does not rule out obstruction in the penile inflow tract, presuming that the veno-occlusive mechanism is intact.

Another purpose may be that the physician wishes to select patients for specific surgical treatments such as penile revascularization or veno-restrictive surgery. For this purpose, PPDU may be used as a first-line test to discriminate between hemodynamic abnormalities in the penile inflow and outflow tract. If abnormal, more invasive tests such as caver-
nosometry or penile angiography may be required. Today it is recognized that the best candidates for revascularization are younger men with isolated lesions in the pudendal artery, the common penile artery, or both, due to pelvic or perineal trauma, rather than older men with more generalized atherosclerotic occlusive disease involving the cavernous artery. The best candidates for venorestrictive surgery are men with anatomic abnormalities such as ectopic veins exiting the cavernous corpora or abnormal communications between the cavernosum and glans/spongiosum. These men may have a history of primary ED, congenital penile abnormalities, urethral surgery, or a blunt trauma to the erect penis, causing a site-specific leak.

Furthermore, it may be important for scientific and clinical reasons to define the cause of ED in groups of patients with a chronic disease, such as diabetes mellitus or renal failure. In these patients, diagnostic testing should focus on the other, less common causes of ED instead of confirming the well-known effects of the chronic illness on the erectile function.

ANATOMY

The paired internal pudendal artery arises from the internal iliac artery and runs outward and downward, leaving the pelvic cavity to enter the gluteal region, where it curves around the ischial spine to enter the ischiorectal fossa. At this point, it runs in the pudendal canal (Alcock’s canal), on the inner surface of the internal obturator muscle. It then passes downward and inward, piercing the urogenital diaphragm to divide into its terminal branches. One of these branches is the common penile artery that divides into four branches: one to the proximal urethral bulb, one to the corpus spongiosum, one to the corpus cavernosum (cavernous artery), and one to the dorsum of the penis (deep dorsal artery). During penile angiography, the identification of the dorsal artery and the cavernous artery is important as a guide to the type of anastomosis required for revascularization. The cavernous artery provides blood to the cavernous body through multiple resistance helicine arteries that open directly into the cavernous sinusoids. Venules located in the subtunical space between the peripheral lacunae and the tunica provide venous outflow from the corpora via the peripheral lacunae.

PATHOPHYSIOLOGY OF VASCULAR ERECTILE DYSFUNCTION

For the sake of convenience, the process of penile erection may be divided into three different phases—arterial response, tumescence, and erectile response. Although the three phases act in concert, each phase has its own pathology and diagnostic tests (Table 1).

The Phase of Arterial Response

An adequate signal to initiate arterial response must be available; psychologic, endocrinologic, and neurologic pathways must be intact. The arterial response is initiated by relaxation of the smooth muscles of the helicine arteries, leading to vasodilatation and, as a consequence of the gradient between systemic arterial blood pressure and intracavernous blood pressure, to a flow into the cavernous sinusoids. In pharmacologically induced erection, the highest flow rates occur within the first minute after injection, depending on the individuals' arterial health. Parameters of quality of arterial response are peak flow velocity and its acceleration time as measured by PPDU, cavernous artery occlusion pressure as measured by cavernosometry, pooling of red blood cells as assessed by scintigraphic evaluation, or increase of cavernous oxygen tension.

The Phase of Tumescence

Relaxation of trabecular smooth muscle facilitates dilatation of the sinusoids. Presuming that arterial inflow exceeds venous outflow, arterial response leads to tumescence: increasing volume and pressure of the cavernous corpora. Parameters for tumescence are length and circumference of the penis.

Phase of Erectile Response

Mediated by complete relaxation of the trabecular smooth muscles and subsequent increasing intracavernous pressure, the subtunical venules are compressed against the tunica albuginea termed veno-occlusion. If the veno-occlusive mechanism is intact, the arterial inflow leads to increase of intracavernous pressure to levels of mean systemic arterial blood pressure (80 to 100 mm Hg), with higher pressures generated by perineal muscular contractions.
INVESTIGATION OF ERECTILE DYSFUNCTION

Table 1. TESTING OF CAVERNOUS HEMODYNAMICS IN DIFFERENT PHASES OF ERECTION

<table>
<thead>
<tr>
<th>Predominant Phenomenon</th>
<th>Phase of Maximal Arterial Response</th>
<th>Tumescence Phase</th>
<th>Phase of Maximal Erectile Response</th>
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<tbody>
<tr>
<td></td>
<td>Maximal Inflow</td>
<td>Increase of Cavernous Volume and Pressure</td>
<td>Maximal Intracavernous Pressure</td>
</tr>
<tr>
<td>Test Modality</td>
<td>Physical Examination</td>
<td>Penile length and circumference</td>
<td>Erection angle</td>
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<tr>
<td></td>
<td>PPDU</td>
<td>Acceleration time</td>
<td>Resistance index</td>
</tr>
<tr>
<td></td>
<td>Rigiscan</td>
<td>Arterial diameter</td>
<td>Diastolic flow velocity</td>
</tr>
<tr>
<td></td>
<td>Cavernosometry</td>
<td>Cavernous arterial occlusion pressure</td>
<td>Radial rigidity</td>
</tr>
<tr>
<td></td>
<td>Gravity cavernosometry</td>
<td>Cavernous oxygen tension (in vivo)</td>
<td>Maintenance flow</td>
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<tr>
<td></td>
<td>Radionuclear scintigraphy</td>
<td>Realtime P02 evaluation</td>
<td>Pressure loss</td>
</tr>
<tr>
<td></td>
<td>Cavernous oxygen tension</td>
<td></td>
<td>Steady-state intracavernous pressure</td>
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</table>

Saenz de Tejada and associates\(^\text{75}\) demonstrated that the tone of the trabecular smooth muscle regulates venous outflow resistance in the corpora. When the smooth muscle is contracted, there is low resistance to outflow. Following complete smooth muscle relaxation the outflow resistance from the corporal bodies increases by approximately 100-fold; it is constant and independent of intracavernous pressure.\(^\text{75}\) Therefore, under physiologic conditions, arterial pressure rather than arterial flow appears to govern penile rigidity. The hemodynamic consequence of incomplete smooth muscle relaxation is the need for higher arterial flows to maintain intracavernous pressures.

Parameters for evaluation of the quality of the veno-occlusive mechanism are diastolic flow velocity and its derivative resistance index as measured by PPDU, maintenance flow, and pressure loss as measured by cavernosometry and xenon-133 washout, as measured with scintigraphy\(^\text{95}\) (Table 2). Clinical parameters of erectile response are erection angle,\(^\text{89}\) buckling force, and radial rigidity as measured with Rigiscan (Dacomed Corporation, Minneapolis, Minnesota).\(^\text{13}\)

PHARMACOTEST

A major breakthrough in the diagnosis of male sexual dysfunction was accomplished with the discovery of pharmacologically inducible erection by intracavernous injection (ICI) of vasoactive agents.\(^\text{85}\) Theoretically, vasoactive substances substitute for the neurotransmitter to activate arterial and sinusoidal mechanisms. Initially, a positive erectile response, defined as a rigid erection, has been presumed to signify a normal vascular status, and neurologic or psychologic factors were considered as a predominant cause for ED. If only partial, short-lived, or no erectile response resulted, vascular ED was presumed.\(^\text{44}\) In clinical practice, however, the interpretation of the pharmacotest appeared to be more complicated. To date, we know that a positive erectile response implies normal veno-occlusive function, but not necessarily normal arterial function. A positive erectile response merely reflexes an intracavernous pressure equal to or greater than 80 mm Hg, whereas the maximum erectile response as determined by the systemic blood pressure could be much higher. Pescatori and co-workers\(^\text{65}\) demonstrated that in 41% of responders, the gradient between systemic and cavernous systolic blood pressure gradient is more that 24 mm Hg. Conversely, a negative erectile response may be due to excessive adrenergic constrictor tone as a result of anxiety.\(^\text{7,50}\) Kim and Oh\(^\text{26}\) demonstrated that the level of norepinephrine in penile blood during the pharmacotest is higher in patients with psychologic ED than in healthy controls or patients with vascular ED. Moreover, in the psychologic group, it appeared significantly higher in nonresponders than in responders. Up to 25% of the nonresponders may show predominance of psychologic factors.

There are several methods to enhance diagnostic accuracy of pharmacotesting: (1) using initial high dosages or redosing, (2) synchro-
Table 2. Reference Values of Parameters of PPDU Recently Published in the Literature

<table>
<thead>
<tr>
<th>Parameter</th>
<th>The Literature (agent, dosage)</th>
<th>Standard Used</th>
</tr>
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<tbody>
<tr>
<td>Peak flow velocity</td>
<td>&gt; 20 cm/s (PGE₁, 20 μg)²⁸</td>
<td>NPT</td>
</tr>
<tr>
<td></td>
<td>&gt; 22 cm/s (papaverine, 12.5 mg)⁴⁸</td>
<td>History</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ Pharm. test*</td>
</tr>
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<td></td>
<td></td>
<td>+ Pharm. test</td>
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<tr>
<td></td>
<td></td>
<td>+ Pharm. test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ NPT^ + VES^†</td>
</tr>
<tr>
<td></td>
<td>&gt; 22 cm/s (papaverine, 25 mg)⁴⁸</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 22 cm/s (papaverine, 50 mg)⁴⁸</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 22 cm/s (pap/phen, 15/0.5 mg)⁴⁹</td>
<td></td>
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<tr>
<td></td>
<td>&gt; 25 cm/s (PGE₁, 10 μg)²¹</td>
<td>Systolic occlusion pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiography</td>
</tr>
<tr>
<td>Acceleration time</td>
<td>&lt; 122 ms (papaverine, 12.5 mg)⁵¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>History</td>
</tr>
<tr>
<td></td>
<td>&lt; 110 ms (papaverine, 60 mg)⁶¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiography</td>
</tr>
<tr>
<td>Acceleration</td>
<td>&gt; 400 cm/s² (pap/phen/PGEx 50 μg)⁸²</td>
<td></td>
</tr>
<tr>
<td>Dilatation</td>
<td>&gt; 21% (papaverine, 12.5 mg)⁴⁹,⁵¹</td>
<td>History</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ Pharm. test</td>
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<td>+ Pharm. test</td>
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<td></td>
<td></td>
<td>+ Pharm. test</td>
</tr>
<tr>
<td></td>
<td>&gt; 70% (PGE₁, 10 μg + (VES))³⁴</td>
<td></td>
</tr>
</tbody>
</table>

* Positive erectile response to pharmacologic stimulation.
* Positive sleep-related erectile response.
* Positive erectile response to visual erotic stimulation.
Adapted from Meuleman EJ: Investigation of erectile dysfunction. Current Opinion in Urology 3:484, 1993; with permission.

nized evaluation of arterial function by PPDU, and (3) enhancement of erectile response by genital self-stimulation,¹¹ vibratory stimulation,²¹,²³ visual erotic stimulation (VES),⁴⁶ or the application of a penoscrotal tourniquet.³³ The most feared complication of pharmacotesting is prolonged erection. The group most prone to prolonged erection are younger patients with nonvascular ED and a better baseline erectile function.³⁷ Therefore, the dose used for initial testing should be adapted to the historic characteristics of the patients and lowered with suspected neurogenic or psychological ED.³⁰

Three different vasoactive agents are used for pharmacotesting: papaverine, papaverine-phentolamine, and prostaglandin (PGE₁). Other drugs such as calcitonin gene-related peptide,⁸⁰ nitric oxide donors,⁶⁸ and vasoactive intestinal peptide (VIP) or combination of drugs are currently under investigation. A pharmacotest, using 50 mg of papaverine, may lead to false-negative erectile response in 25% of nonselected impotent men, whereas prolonged erection may occur in 5.3%.⁶⁷ In a multicenter study comparing papaverine, papaverine-phentolamine, and PGE₁, PGE₁ emerged as the most accurate diagnostic drug, with an overall erection rate of 74% and a prolonged erection rate of only 0.1%.⁶⁷ Recently, in a review of the literature, Jüinemann and Alken²³ found the following rates of prolonged erections during diagnostic work-up: papaverine 9.5%, papaverine-phentolamine 5.3%, and PGE₁ 2.4%. Nonresponders bear a high probability of a vascular origin with a predominance of veno-occlusive insufficiency.²³

In view of a treatment-directed instead of an etiology-directed approach, at our institution, a low-dose ICI test is combined with VES. Additionally, a postinvestigation questionnaire (PIQ) is used to rate erection following investigation when the patient has left the office. Of the 90 patients studied, 11% showed adequate erections to ICI alone (7.5 mg to 0.25 mg papaverine-phentolamine) and 67% to ICI + VES,
whereas 23% of the in-office nonresponders reported adequate erections after leaving the office. No prolonged erections were encountered. A negative response is followed by repeated tests of up to a maximum dose of 30 mg: 1 mg papaverine-phentolamine in an auto-injection trial at home. We believe that under these circumstances, the pharmacotest will provide an ultimate assessment of the patients' maximal responsiveness to treatment by intracavernous auto-injection and may make more invasive diagnostic techniques redundant.

PHARMACOPENILE DUPLEX ULTRASONOGRAPHY

The development and application of sonographic equipment have grown tremendously since Gaskell introduced a Doppler device for evaluating penile blood pressure in 1971. Early Doppler systems were nondirectional, that is, no distinction could be made between blood moving away from the probe and blood moving toward the probe. Nor could a distinction be made between the cavernous and dorsal arteries. The systems could only detect presence of flow and were used in measurements of penile arterial pressure. In 1980, the pulsed-Doppler device was introduced for evaluating erectile dysfunction. This device can detect the direction of blood flow and uses various depths of sampling. Coupling of the device to a spectral analyzer made it possible to obtain a printed Doppler velocity waveform of the vessel under study. In the latest development, PPDU, blood flow velocity waveform analysis, and ultrasonographic imaging are combined to assess anatomical and functional parameters of pharmacologically stimulated penile circulation simultaneously: duplex ultrasonography.

Technique of PPDU

A duplex-scanner with color flow imaging possibilities is used. B-mode color images and Doppler spectra are obtained with a 7.5 MHz linear-array transducer. B-mode ultrasonography provides visualization of cavernous arteries and bodies (Fig. 1). Electronic cursors are used to measure diameters of cavernous arteries in longitudinal projection in the proximal penile shaft up to an axial resolution of 0.1 mm (Fig. 2). By using color image as a guide to the localization and direction of blood flow, the Doppler sample volume cursor is placed in the cavernous artery as proximal as possible in the infrapubic region, and the Doppler angle correction cursor is adjusted to match the correct axis of flow. The resulting angle-corrected Doppler spectrum is displayed on the monitor, and acceleration time, peak flow velocity, and end-diastolic flow velocity are measured directly from the recorded velocity tracing. That information is used to calculate resistance index (RI): \[
RI = \frac{\text{peak flow velocity} - \text{diastolic flow velocity}}{\text{peak flow velocity}}
\]
Knowledge of these parameters provides an estimate of penile blood flow and is a useful indicator of arterial inflow capacity and venous outflow.

Figure 1. The anatomy of the infrapubic region and course of the cavernous artery. The transducer is placed longitudinally or transversely across the dorsal surface at the base of the penis and angled inferiory towards the penile crus. (From Meuleman, EJ: The value of combined papaverine testing and duplexscanning in men with erectile dysfunction. Int J Impotence Res 2:37, 1990; with permission.)
Furthermore, pathologic conditions such as vascular calcifications or fibrosis associated with Peyronie’s disease can be located (Fig. 4). Additionally, PPDU may be helpful in staging penile carcinoma (Fig. 5).

Since Lue and associates introduced PPDU as a diagnostic tool, it has become the first-line test to define vascular ED. Initially, it was used to assess arterial hemodynamic disorders, but recently, the use of PPDU as a means of evaluating veno-occlusive function is gaining acceptance. It has replaced the measurement of penile blood pressure, whereas pudendal angiography and cavernosometry are preserved as second-line tests for patients in whom surgical repair is considered.

In PPDU, the sampling location and interval after pharmacologic stimulation are critical. In healthy controls, there is a mean reduction of flow velocity between the crural and distal subcoronal cavernous artery of about 20%, whereas in patients with peripheral arterial occlusive disease, velocity may be reduced 50%. With respect to location, the consensus in the literature is that velocity tracings should be obtained in the most proximal part of the cavernous arteries, for example, in the crural part. With respect to timing, the consensus is that arterial response is to be determined in the phase of erection with highest flow rates, for example, in the first minutes following intracavernous pharmacologic stimulation. Following the original study by Lue and associates, a peak flow velocity < 25 cm/second and a diastolic flow velocity of less than 75% have been considered to indicate arterial disease. To date, apparently cavernous arterial dilatation is an unreliable parameter and measurement of the single Doppler parameter peak flow velocity is an inadequate discriminant of arterial disease. Current parameters are peak flow velocity and acceleration time. Mellinger and co-workers have added the category of penile blood flow acceleration (peak flow ve-

Figure 2. Longitudinal ultrasonographic image of the cavernous body through the plane of the artery. To the left is the infrapubic region.

Figure 3. Doppler spectrum analysis. a-b/a = resistance index; a/c = acceleration; a = peak flow velocity; b = diastolic flow velocity; c = acceleration time. (From Meuleman EJ, Bemelmans BLH, Van Asten WN, et al: Assessment of penile blood flow. J Urol 147:51–56, 1992; with permission.)
Figure 5. A longitudinal B-mode image of the distal part of the cavernous body showing a penile carcinoma (arrow). (continued, consistent with Peyronie's disease. AC = cavernous artery.)

Figure 4. A transverse B-mode image of the cavernous body showing fibrosis of the medio-dorsal bulbar disfigure.
locity: acceleration time) to the list of duplex data (Fig. 3). Generally, a dampened velocity waveform, with long systolic acceleration time and a low peak flow velocity, indicates arterial disease (Figs. 6 through 8).

In the literature, controversies exist on reference values. In Table 1, the reference values published in the period of review are listed. The differences may be contributed to the different standards that were used for the selection of patients and healthy controls. Moreover, the large ranges of values may indicate that there is a large surplus capacity in arterial supply. This means that the arterial supply must be severely compromised before it becomes a predominant cause of ED.61 It should be noted that arterial response has been shown not to depend on the type of any currently used vasoactive agent nor on external factors such as anxiety and stress, as long as supraphysiologic dosages are used.19,49 Recently, Porst68 demonstrated that arterial response after ICI of a physiologic dose of a nitric oxide donor (linsidomine chlorhydrate) is a third less than after injection of a supraphysiologic dose of PGE1.

Veno-occlusion and erectile response are two closely related phenomena. In fact, veno-occlusive function is presumed sufficient when an adequate erectile response occurs. Because cavernous venous outflow is not quantifiable by PPDU, veno-occlusive function is indirectly estimated by assessing cavernous venous resistance in the phase of maximal erectile response. Parameters are diastolic flow velocity32 and its derivative RI. In our opinion, RI is the superior parameter because the most important variable associated with the process of sampling, the probe-vessel angle, is filtered out in the formula $\text{RI} = (\text{peak flow velocity} - \text{diastolic flow velocity}) / (\text{peak flow velocity})$. Following pharmacologic stimulation, the value of RI adjusts to a level depending on intracavernous pressure. As soon as intracavernous pressure equals or exceeds systemic diastolic blood pressure, diastolic blood flow velocity will equal zero and the value for RI equals 1 (Fig. 9). As long as intracavernous pressure remains below systemic diastolic pressure, diastolic flow will persist and the value for RI will remain below 1 (Fig. 10). It has been estimated that an intracavernous pressure of 80 to 100 mm Hg is necessary for full erection.45 As a consequence, a postinjection value of 1 indicates full erection, whereas a postinjection value < 1 indicates incomplete erection. In conclusion, veno-occlusive dysfunction is characterized by RI < 1 in the phase of maximal erectile response.51

One aspect in the evaluation of the veno-occlusive mechanism is particularly troublesome: in contrast with arterial response, erectile response is influenced by the type and dosage of the vasoactive agent and by the psychologic impact of the testsetting on the patient. This may lead to a false diagnosis of veno-occlusive dysfunction. This may be decreased by starting with a high dose of vasoactive agent(s) or by repeated dosing.60 Both strategies, however, bear the risk of prolonged erection. Furthermore, the incorporation of visual sexual stimulation, genital self-stimulation, or vibrotactile stimulation may decrease psychologic inhibition and enhance erectile response. Our experience is that these additions interfere with PPDU. We found the patient’s self-report on erectile response and his experience of a satisfactory sexual intercourse following the examination to be the most valid test for veno-occlusive sufficiency.86

Figure 6. The hemodynamic effect of an arterial stenosis. Note the dampened velocity waveform with long acceleration time distally of the stenosis.
CAVERNOSOMETRY

Cavernosometry is the primary modality available for quantifying and mapping of veno-occlusive dysfunction in men with erectile failure, although its ability to differentiate between the different types of veno-occlusive dysfunction is limited. Because it is an invasive test, at our institution it is preserved for selected patients believed to have veno-occlusive dysfunction, in whom surgical repair directed at limiting venous outflow is considered. Usually, these are younger patients with a low resistance to venous outflow due to anatomic ab-
normalities such as ectopic veins or abnormal communications between the corpora and the spongiosum. These patients typically achieve some tumescence with sexual stimulation, but they usually cannot obtain enough rigidity for satisfactory vaginal intromission. They may have a history of perineal trauma or a congenital malformation of the penis, such as hypospadias or penile curvature. Nocturnal penile tumescence (NPT) studies\textsuperscript{76} show a normal frequency of rapid eye movement associated episodes with increase in penile circumference, whereas rigidity of erection is deficient in degree, duration, or both. On PPDU, they may have a normal arterial response but persisting diastolic flow in the phase of maximal erectile response.\textsuperscript{47,48} Veno-occlusive dysfunction may be seen as a
multifactorial condition, with each potential mechanism interdependent on others. Globally, it can be classified into different pathophysiologic subtypes: (1) Anatomic abnormalities such as large and ectopic veins exiting the cavernous corpora. In younger men this is probably congenital in origin, whereas in older men, this is caused by alterations of the tunica albuginea, for example, in Peyronie's disease (especially, Peyronie's plaque excision with heterotopic or dermal grafting can provoke veno-occlusive dysfunction). Or it could be caused by abnormal communications between the cavernous and glans/spongiosum. This may be congenital, posttraumatic, or due to priapism surgery. (2) Functional abnormalities, typified by a limited capacitor function of the corpora. This may be due to either impaired relaxation of heightened cavernous smooth muscle contractility. Impaired relaxation may occur in patients with damaged parasympathetic dilatory nerves, such as in diabetes mellitus. In these cases, neurogenic ED presents with veno-occlusive dysfunction. Recently, much attention is focused on disturbed intercellular communication as a possible mechanism of veno-occlusive dysfunction. It should be noted at this point that disturbed relaxation may be the sole effect of anxiety due to excessive adrenergic constrictor tone, such as in anxiety states. Therefore, psychologic ED such as honeymoon ED or widowers ED may present with veno-occlusive dysfunction. Other causes for impaired cavernous veno-occlusion may be structural abnormalities of the fibro-elastic components of the trabeculae, as a result of aging, diabetes mellitus, vascular disease surgery, or trauma, and structural abnormalities of the smooth muscle cells.

Venous resistance is regulated by the tone of the trabecular smooth muscle. Relaxation of smooth muscle allows expansion of the corpora with accumulation of volume under pressure, enabling the penis to act as a capacitor. After complete relaxation venous resistance increases ± 100-fold, it is constant and independent of intracavernous pressure. In cavernosometry, venous outflow resistance is assessed by determining the intracavernous flow rate required to sustain erection (intracavernous pressure > 80 mm Hg) in a state of controlled complete cavernous smooth muscle relaxation. Since its introduction by Newman and colleagues in 1964, several modifications of technique have evolved. In the earliest publications, a rollerpump was used to regulate the infusion flow rates. In 1988, Puech Leao and associates introduced an alternative technique that required less complicated technology and was less expensive: gravity cavernosometry. Instead of using a rollerpump, a simple infusion set was used to generate a steady infusion pressure. Although the concepts of veno-occlusive function and cavernosometry seem to be straightforward, method and interpretation of results have long been subjects of debate. The need for controlled complete smooth muscle relaxation has especially frustrated physicians performing cavernosometry. They were confronted by two critical questions: (1) What is the evidence that complete smooth muscle relaxation has occurred? (2) How can one induce complete muscle relaxation after initial (partially failed) stimulation? Anxiety and embarrassment in the nonsexual situation with little privacy appeared to be almost incompatible with a state of drug-induced complete cavernous relaxation. Inevitably, cavernosometry has overestimated the degree of structural veno-occlusive dysfunction. This and the inability to identify individual subtypes of veno-occlusive dysfunction account for the disappointingly low long-term success rate of venous restrictive surgery (30% to 50%). Recently, Saenz de Tejada and Goldstein have developed a promising new method that seems to enable cavernosometry under conditions of known corporeal smooth muscle relaxation, making it more reliable for clinical practice.

CAVERNOGRAPHY UNDER CONTROLLED COMPLETE SMOOTH MUSCLE RELAXATION

The investigator should make every effort to minimize inhibiting factors by creating an atmosphere of privacy, for example, by limiting the number of personnel in the room and using infusion fluids at body temperature. The patient is placed supine on the fluoroscopy table. Three milliliters of 1% xylocaine is administered to the subcutaneous area overlying the dorsal subcoronal area. Once anesthesia has been established, two 19-gauge needles, previously flushed with heparinized saline, are introduced intracavernously. Correct placement is assured by flushing the needles with saline. The saline should pass easily, there should be no subcutaneous bleb forming, and no saline should be seen in the urethral meatus. Then, one needle is connected to the infusion source, and the other needle is connected to a pressure monitor. At this stage, correct placement of the needle can be confirmed by observation of the
typical pressure spikes provoked by squeezing of the penis or straining of the patient. Blood pressure and pulse are monitored following intracavernous administration of vasoactive agents. Systemic side effects are characterized by a cardiovascular problem (syncope or hypotensive events associated with pallor, dizziness, sweating). These side-effects, however, are rather infrequent and are most likely to occur when high-dose papaverine monosubstance is used. Systemic side effects with PGE₁ have not been observed. When symptoms develop, the test is stopped and the legs of the patient are elevated.

The method of cavernosometry under controlled complete cavernous smooth muscle relaxation is recently described by Saenz de Tejada and Goldstein following their observations in an animal model. The experience with the clinical application has not been published in the literature yet, except for a short communication of Udelson and associates. The procedure is started with the injection of a combination of 30 mg papaverine and 1 mg phentolamine (Androskat, BYK Nederland BV, Zwanenburg, the Netherlands). In our institution, this particular combination is chosen because it recently has been approved for diagnostic and therapeutic purposes in the Netherlands. Other investigators use trimixes or even quadrimixes containing papaverine, phentolamine, PGE₁, and atropine. Succeeding the ICI of these vasoactive agent(s), steady-state intracavernous pressure is awaited. Then, depending on intracavernous pressure, an infusion pump regulated by an intracavernous pressure feedback mechanism is used to measure flow necessary to maintain intracavernous pressures at 30, 60, 90, 120, and 150 mm Hg. The state of complete cavernous relaxation is characterized by a linear relationship between infusion rate and these intracavernous pressures. If a nonlinear relationship is demonstrated, relaxation is considered incomplete. Incomplete relaxation is induced to be complete with repeated administrations of vasoactive agent(s) (redosing). Most patients may require a second and even third dosage to attain full smooth muscle relaxation.

In the literature, several parameters are used to measure venous resistance, such as maintenance flow (MF), pressure loss (PL), and pressure volume response (PVR).

**Maintenance Flow**

To date, maintenance flow is considered as the most important parameter and involves the recording of the flow required to maintain intracavernous pressure at a level of 150 mm Hg. This particular level is chosen because it is suprasystolic and therefore isolates the maintenance flow from any component of cavernous arterial inflow. The rate of infusion flow required to maintain the intracavernous pressure at 150 mm Hg is defined as MF. In the era before controlled complete smooth muscle relaxation, different reference values for MF were quoted in the literature. To date, we know that those differences were the result of the variability of smooth-muscle relaxing effect of different vasoactive agents used among investigators, the different circumstances of cavernosometry, and the different selection criteria for healthy controls. In patients who have a full erectile response to intracavernous pharmacologic agents, it has been observed that MF is less than 3 mL/minute. Therefore, 3 mL/minute can be considered as a cutoff value. One should keep in mind, however, that so far no studies have been performed evaluating the relationship between age and venocavernous resistance in a state of controlled smooth muscle relaxation.

If MF is considered to be abnormal and it can be normalized by placement of a tourniquet at the base of the penis, the abnormal drainage may be expected to be located at the level of the deep dorsal vein, glans penis, corpus spongiosum, or superficial dorsal veins along the shaft of the penis. If MF is normalized by the placement of perineal compression, then a subsequent cavernosography will demonstrate abnormal drainage into the subsympathetic deep dorsal, cavernous, and crural veins.

**Pressure Loss**

After intracavernous pressure has been set at a steady-state equilibrium of 150 mm Hg, infusion is stopped and pressure loss (PL) over a period of 30 seconds is determined. When veno-occlusive dysfunction is present, there is a low venous-outflow resistance resulting in a rapid fall in intracavernous pressure. A PL of less than 1.5 mm Hg/second is considered to be normal.

**Pressure Volume Response**

Saline infusion is started at a rate of 60 mL/minute. If intracavernous pressure (ICP) does not reach 75 mm Hg after 1 minute, infusion is stopped and steady state is awaited. Then perfusion is restarted at a rate of 120
mL/minute. Infusion is stopped as soon as ICP has reached 200 mm Hg. Pressure volume response (PVR) is then calculated by the formula: \( PVR = \frac{\text{ICP increase}}{\text{volume infused}} \). Based on a study in 36 impotent males and 2 healthy volunteers, using the combination of 60 mg papaverine and 1 mg phentolamine, Bookstein and associates selected a \( PVR > 1 \) mm Hg/mL as criterion of normal veno-occlusion. Using 50 mg of papaverine in 96 males, we found a reference \( PVR \) of 1.7 mm Hg/mL. In the same study, comparing different parameters of cavernosometry, PL \( PVR \) and PL appeared to be least reliable. This is explained by the fact that both parameters are not only dependent on the tissue properties of the relaxed smooth muscle fibers and the fibro-elastic elements in the trabeculae and tunica albuginea but also on cavernous arterial pressure.

**Gravity Cavernosometry**

In gravity cavernosometry, the inflow needle is connected to a column of heparinized normal saline at body temperature. Free-flow delivery is checked by a droplet-counting chamber that is incorporated in the system. In gravity cavernosometry, the state of complete smooth muscle relaxation is demonstrated by a linear relationship between steady-state intracavernous pressure and different columns of heparinized normal saline (40, 80, 120, and 160 cm H2O). Once complete relaxation is established, intracavernous pressure at a column of 140 cm H2O is determined. The closer intracavernous pressure equals infusion pressure, the better the status of the veno-occlusive mechanism. In a group of normal controls, composed of psychologic impotent patients, Puech-Leao found that at a pressure of 140 cm H2O, intracavernous pressure is higher than 110 mm Hg after cavernous relaxation with 100 mg papaverine. In a study comparing gravity and pump cavernosometry, it appeared that intracavernous pressure at a column of 160 cm H2O and maintenance flow showed a good correlation and have the highest diagnostic value for veno-occlusive dysfunction. To date, no results of gravity cavernosmetry performed under condition of controlled complete smooth muscle relaxation are available in the literature.

**Cavernosography**

If cavernosometry, performed in a proven state of complete smooth-muscle relaxation, suggests that significant veno-occlusive dysfunction is present, the anatomic site of leakage can be demonstrated by intracavernous infusion of contrast. After cavernosometry has been completed, a nonallergic contrast medium of low osmolality (Omnipaque 240 mg/mL, Nycomed, Breda, the Netherlands) is used to infuse the cavernous body. The anatomic site of draining veins is then real-time visualized fluoroscopically. When a steady-state intracavernous pressure of 90 mm Hg is reached, anteroposterior and right and left oblique films are taken. In veno-occlusive dysfunction, veins are visualized draining from the cavernous body during erection, in the glans, corpus spongiosum, the deep dorsal, cavernous, and crural veins. At the end of the study, the contrast medium is allowed to drain from the cavernous body and the butterfly needles removed. More than one site is found in most of the patients, with the deep dorsal and cavernous veins as the most common combination.

**Cavernous Artery Occlusion Pressure**

A method of functional evaluation of the cavernous artery in the dynamic state is by measuring its occlusion pressure, at the time of cavernosometry. A Doppler ultrasound transducer probe is placed over the left and right lateral aspects of the cavernous body at the base of the shaft to record the respective cavernous artery pulsating flows. The cavernous body pressure is elevated above the cavernous artery systolic occlusion pressure by heparinized saline infusion. The infusion is terminated as the cavernous artery pulsating flow disappears. As the cavernous body pressure diminishes, the cavernous artery pulsating flow is reestablished. The cavernous artery systolic occlusion pressure is defined as the cavernous body pressure when cavernous artery pulsating flow is reestablished. This value is compared with the brachial artery systolic occlusion pressure recorded during this phase. Based on observations in a normal physiologic group, Padma Nathan and Goldstein defined reference values by the gradient between the brachial artery systolic occlusion pressure and cavernous artery systolic occlusion pressures: a difference of over 36 mm Hg is considered as abnormal cavernous artery hemodynamic function.

**PENILE ANGIOGRAPHY**

Ginestie and Romieux first performed selective penile angiography on impotent patients. At our institution, penile angiography is
performed in selected cases of younger patients believed to have isolated arterial disease, in whom surgical repair is considered. The study is used to define the anatomic pattern of arterial occlusive disease and allows the planning of an appropriate vascular surgical approach. In the majority of patients, anatomic variations of the penile inflow tract can be demonstrated.

NUCLEAR MEDICINE IMAGING

Scintigraphic evaluation of ED was introduced and developed by Shirai and Nakamura\(^7\)\(^8\) in the early seventies. This method did not find widespread clinical application. The major approaches have been either blood pool studies, with \(^99\)mTc-labeled red blood cells\(^18\)\(^79\) or washout methods,\(^94\) chiefly using xenon-133.\(^95\) A new dynamic radioisotope technique is based on the simultaneous quantification of the change of blood volume and venous outflow, using a combination of blood pool and washout studies.\(^54\)

NEW EXPERIMENTAL TESTS

Penile Biopsy

Recently, attention has been focused on (ultra)structural investigation of cavernous tissue obtained by needle biopsy as a tool in the diagnosis of disease of the cavernous body.\(^52\)\(^90\)

Penile Extensibility

Penile extensibility is correlated with age and erectile function\(^4\) and has been proposed as a method to assess the elasticity of the tunica albuginea as a function of veno-occlusive capacity.\(^58\)

Cavernous Oxygen Tension

The development of unbreakable, small-caliber oxygen-sensitive probes has advanced the clinical application of real-time evaluation of cavernous oxygen tension.\(^59\)

TREATMENT OF PROLONGED ERECTION

The most common complication during the diagnostic work-up and especially during cavernosometry is pharmacologically induced prolonged erection. Not all pharmacologically induced prolonged erections require a specific treatment because penis detumescence generally occurs within a few hours. Lue and associates\(^41\) demonstrated that in pharmacologically induced prolonged erection, blood gas values manifest inadequate blood supply to the erectile tissue after 6 hours.

In case duration of erection exceeds 6 hours, the cavernous corpora are drained to decrease pressure and an adrenergic agonist is injected intracavernously to induce cavernous smooth muscle contraction, effective venous drainage, and restriction of arterial inflow. We use 10 \(\mu\)g of adrenaline. The correct dose is prepared by adding 1 mg adrenaline to 100 mL normal saline, to make a solution of 10 \(\mu\)g adrenaline/1 mL. After a compressive bandage has been applied, the penis is fixed to the innerdorsal site of the thigh. After 30 minutes, the bandage is removed. In case an erection has recurred, the procedure is repeated. The blood pressure and pulse should be monitored during and following adrenergic agonist administration.

SUMMARY

To date, several accurate tests for diagnosing vascular ED may be chosen. It is necessary to be well aware of the purpose of testing: global assessment of erectile capacity in preparation for auto-injection therapy, or detailed assessment of arterial and erectile response in preparation for surgical treatment. Pharmacotesting may be sufficient for the majority of patients. Other, more invasive tests are reserved for preparing surgical treatment or scientific studies.

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