Review

Erectile dysfunction – overview from a cardiovascular perspective

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Summary: Erectile dysfunction (ED) is an evolving health problem with growing incidence in the ageing male population with potentially predictive value for cardiovascular and other chronic diseases. ED shares the common cardiovascular risk factors. The aetiology of ED is numerous including neurogenic, psychogenic, arteriogenic, and venogenic reasons. The origin of arteriogenic ED is frequently atherosclerosis. Patients not adequately responding to conservative measures including oral medication are often referred to further vascular diagnostics and therapy. At present, the refinements in endovascular therapy allow for minimal-invasive revascularization of erection-related arteries. The role of endovascular therapy in the complex framework of the multifactorial causes of ED requires further scientific scrutiny.

Keywords: Erectile dysfunction, arteriogenic, diagnostic, endovascular therapy

Introduction

Erectile dysfunction (ED) has become an increasing health problem with growing prevalence in the ageing male population. Its prevalence is age-dependent and ranges from 2% in younger (< 40 years) to 86% in older men (> 80 years) [1]. Worldwide, more than 150 million men are expected to suffer from ED [2, 3]. In addition to the patients' psychological strains, ED is frequently representative for underlying atherosclerosis. Therefore, it is not surprising that ED shares the common cardiovascular risk factors. Furthermore, ED is often associated with other chronic diseases i.e. coronary artery disease [4–7] or obstructive sleep apnoea syndrome [8, 9]. Montorsi et al. reported a 70% prevalence of ED in a consecutive series of 300 patients presenting with acute chest pain and angiographically documented coronary artery disease [4]. In addition, ED patients have an increased risk (relative risk: 1.48 [95%-CI: 1.24–1.74]) to suffer from cardiovascular disease when compared to non-ED patients. [7]. Thereby, younger ED patients (< 40 years) are even more prone to experience a cardiovascular event with an incidence of > 7 times when compared to a healthy control group [10]. Similarly, an ED prevalence of > 60% was reported in patients presenting with obstructive sleep apnoea syndrome [8, 9].

In line with these observations, there is an increasing interest in ED for healthcare providers, not only for its treatment but also for its association with other underlying diseases. The present article aims to provide a comprehensive introduction to the subject and to give an overview on the disease of ED from a cardiovascular perspective.

Definition

ED is defined as the inability to achieve and/or maintain penile erection for a satisfying sexual intercourse [11]. The best validated and sensitive tool to systematically assess ED in men is the International Index of Erectile Function (IIEF) score [12]. The IIEF-15 score consists of fifteen questions (ESM 1, ESM 2). Thereby, a cut-off of 21 points was shown sensitive to discriminate ED patients from healthy individuals [12, 13].

Anatomy and pathophysiology

The penis consists of the paired dorsal corpora cavernosa and the ventral corpus spongiosum, which surrounds the urethra and is connected to the glans penis. The corpora cavernosa are composed of smooth muscle cells and con-

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nective tissue and build-up blood-filled spaces. These expandable spongy formations are covered with the dense tissue tunica albuginea. Arterial supply to the penis is provided by the paired penile arteries arising from the internal pudendal artery, a branch of the internal iliac artery. The penile artery has four terminal branches: the cavernous, dorsal, bulbar, and urethral arteries. Venous outflow results from post cavernous venules, which form emissary veins and drain into the cavernous, the deep dorsal, and the superficial dorsal veins. The innervation of the erectile tissue is provided by parasympathetic, sympathetic, and somatic nerves.

The stimulus for erection either comes from the *central nervous system* (supraspinal centres) or from the *peripheral nervous system* by mechanical stimulation of the dorsal nerve of the penis. Penile erection results from a complex cascade of nervous, vascular, hormonal, and psychological actions. During the flaccid state, blood flow to the penis is limited via anti-erectile neural inputs, particularly mediated by sympathetic efferents. By mechanical or psychological sexual stimulation parasympathetic tracts get activated and erectile response is initiated via neurotransmitter release onto postsynaptic smooth muscle cells. This includes the release of several neurotransmitters from the cavernosal nerve terminals and endothelial cells: nitric oxide (NO), vasoactive intestinal polypeptide, acetylcholine, and several prostaglandins.

Of these, NO is considered to be the most important neurotransmitter for penile erection. After diffusion into smooth muscle cells, NO activates the soluble guanylyl cyclase enzyme. This induces the production of the second messenger cyclic guanosine monophosphate (cGMP), which leads to a decrease in intracellular Ca2 and to relaxation of the smooth musculature of the arteries. Consequently, arterial perfusion to the corpora cavernosa is increased while compression of the subtunical venous plexus reduces venous outflow (veno-occlusive mechanism). As a result of these mechanisms, the intracavernous pressure increases up to three to four times leading to penile erection. After ejaculation, neural adrenergic fibres release noradrenaline. This promotes the phosphodiesterase type-5 (PDE-5) enzyme to hydrolyze cGMP to the inactive guanosine monophosphate. As a result, intracellular Ca2+ rises, smooth muscles contract, and pressure decreases by restored venous outflow.

Based on these physiological mechanisms, reasons for ED can be classified as *neurogenic*, *arteriogenic,* and *venogenic*. Thereby, neurogenic causes (i.e. central nervous system, psychological problems) include any problem with initiating the subsequent vascular reactions. Arteriogenic problems involve any reason for not adequately filling the penis with blood, and any failure of the veno-occlusive system is referred to as a venogenic problem. In these patients, dysfunction of the corporal smooth muscle cells leads to incomplete resistance of the blood outflow from the corpora [14]. This results in venous leakage, which is frequently associated with an incomplete erection.

The association of ED and cardiovascular events is based on the common pathophysiological mechanisms of endothelial dysfunction [15], inflammation [16], and low testosterone levels [15, 17].

Non-invasive diagnostic work-up

Patient history

The most important tool of non-invasive ED diagnostic is to obtain a proper patient history. General anamnesis focuses on cardiovascular risk factors, family history of ED, and a description of the functional problems associated with ED. Thereby, regular nocturnal and early morning erections are of predictive value to rule out vasculogenic ED [18]. Nocturnal penile tumescence monitorings are performed by nocturnal electrobioimpedance volumetric assessment [19]. Of note, nocturnal and early morning erections come along with rapid eye movement sleep, which decreases in ageing men [20, 21]. Furthermore, the thorough patient history includes the IIEF questionnaire (ESM 1, ESM 2). In addition, a history of drug-intake is required (i.e. antihypertensive medication, antidepressants, antiandrogenic agents) as well as the already applied therapeutic strategies (i.e. phosphodiesterase inhibitors, vacuum pump, intracavernous injection).

Clinical examination

This involves examination of the genitourinary system including palpation of the prostate and searching for signs of hypogonadism (body hair, characteristics of other men in family, temporal hair recession, full male musculature, deep voice, small testes (< 20 ml), small phallus (< 8 cm), gynecomastia, and length of the long bones). Furthermore every patient must be given a neurological status and an examination of the peripheral pulses, oscillometry, and ankle-brachial index (ABI). The value of the ABI assessment in patients with suspected ED is conflicting. ED was shown to be an independent predictor of peripheral artery disease (PAD) defined as an ABI < 0.9 [22]. On the other hand, an ABI of < 0.9 is of limited predictive value to diagnose ED in the general population [23]. Only in diabetic and cardiovascular high-risk patients (Framingham Risk Score), an ABI of < 0.9 may be associated with and be predictive for ED [23]. In line, cardiovascular risk stratification in patients with suspected ED using the Framingham Risk Score is promoted by some in order to determine the diagnostic work-up [24].

Laboratory testing

Men with a diminished libido may suffer from low serum testosterone and may benefit from hormone replacement. Diagnose and therapy should be performed in

close collaboration with endocrinologist and prostatic cancer should be excluded. Laboratory testing incorporates checking for hypothalamic-pituitary and/or gonadal disorder. The general laboratory testing includes: LH, FSH, testosterone levels, and GnRH. In addition, a glucose and lipid profile testing is recommended. Of note, testing of testosterone levels is particularly recommended in patients with failed PDE-5 inhibitor treatment [24]. Testosterone levels < 200 ng/dl are considered low and supplementation may be considered [25].

Medical treatment

As in other cardiovascular pathologies, lifestyle modifications are important. Many men with erectile dysfunction may benefit from smoking cessation, weight loss, physical activity, reduction of alcohol intake/stop drug consumption or solve relationship problems [26].

Nevertheless, therapy should be customized. If there is no success in spite of lifestyle modifications, oral medications are often the next approach for erectile dysfunction therapy. There are oral substances available to treat psychogenic ED i.e. yohimbin, an alkaloid with α-2 antagonistic effects in the central nervous system. However, these medications are not recommended by the German (DGU: Deutsche Urologie Gesellschaft) and the American Urological Association (AUA). Testosterone supplementation is controversial but may be considered in patients with low testosterone levels presenting concomitantly with abnormal nocturnal erections [25, 27].

For vasculogenic ED, PDE-5 inhibitors are the most commonly used medications and recommended as first-line treatment unless there are contraindications including myocardial or cerebral infarction within six weeks, angina pectoris, intake of nitrate drugs, cardiac arrhythmia, retinitis pigmentosa, or renal and hepatic insufficiency [28]. They are chosen depending on the onset of action, duration of action, and possible side effects.

To avoid long-acting side effects, patients without experience should receive substances with short duration of action. However, about 50 % of patients would not be responsive. But before being classified as non-responders, eight attempts should be carried out. There are different PDE-5 inhibitors on the market varying slightly in half-life but sildenafil (Viagra®) is the most frequently used and prescribed agent.

If oral therapy is not successful or appropriate, there are non-oral treatment options such as intracavernous self-injections, penis pumps or surgical methods.

However, it is important to keep in mind that ED may present as a side effect of concomitant medications such as beta blockers for antihypertensive therapy. Several studies reported impaired sexual function in patients taking beta blocker medication [29, 30]. In patients with concomitant and indicated beta blocker therapy, switching to a novel third-generation β-1 blocker, e.g. nebivolol, with a greater degree of selectivity for β-1 adrenergic receptors is reasonable. Compared to other agents, nebivolol has a very low risk of sexual side effects [31]. Some reports even attribute nebivolol with positive effects on erectile function based on favorable NO modulation [32].

In addition, the effects of statin therapy in ED patients remain conflicting [33]. In animal models, statin therapy was shown to have beneficial effects on the endothelium and to increase NO concentrations [34]. In line, it is hypothesized that statin therapy may improve the NO mechanism and thus, increase the efficacy of concomitant PDE-5 therapy [35–37]. However, statin therapy was also shown to impair testosterone synthesis with adverse effects on penile erection [38]. Overall, statin therapy alone [39], as well as in combination with PDE-5 inhibitor therapy, was shown to improve the sexual health related quality of life in ED patients but may not be considered an erectogenic drug [40]. Nevertheless, it is suspected that statin therapy may improve the efficacy of PDE-5 inhibitor therapy in patients with endothelial dysfunction [40].

In case of non-responsiveness to all these treatment strategies, no evident reason for any adverse effects of co-medication and reasonable suspicion of vasculogenic ED, further diagnostics and invasive therapy may be considered. Figure 1 provides an algorithm for diagnostics in ED patients.

Arterial imaging and endovascular therapy of arteriogenic ED

Arteriogenic ED may affect different arteries and was shown to present with a great variety of lesion patterns. In patients with suspected arteriogenic ED, duplex ultrasound is recommended for primary arterial examination. However, duplex sonography may be challenging and also limited to the common and proximal internal iliac arteries as well as the penile arteries. The pudendal arteries are not visualizable at all but can only be assessed by indirect examination of the distal penile artery. Proper duplex ultrasound examination of the penis artery (profound penis artery) is only possible after intracavernous injection of alporostadil (PGE-1). In general, the application of 5 ug PGE-1 is sufficient for proper stimulation. However, in ED patients with an underlying vasculogenic disorder, doses of 10–20 ug may be necessary to attain a proper erection. In the erected penis, a peak-systolic velocity > 0.3 m/s and a resistance index > 0.8 in the penile artery are considered normal [41]. An increased end-diastolic velocity (> 0.05 m/s) implying low arterial resistance is considered to indicate a problem with the penile veno-occlusive mechanism [42].

In patients with suspected arteriogenic ED, a computed tomography angiogram (CTA) or magnetic resonance angiography (MRA) is recommended for further distinction of macro versus microangiopathic disease. Based on the imaging, diagnostic angiography, and percutaneous revas-

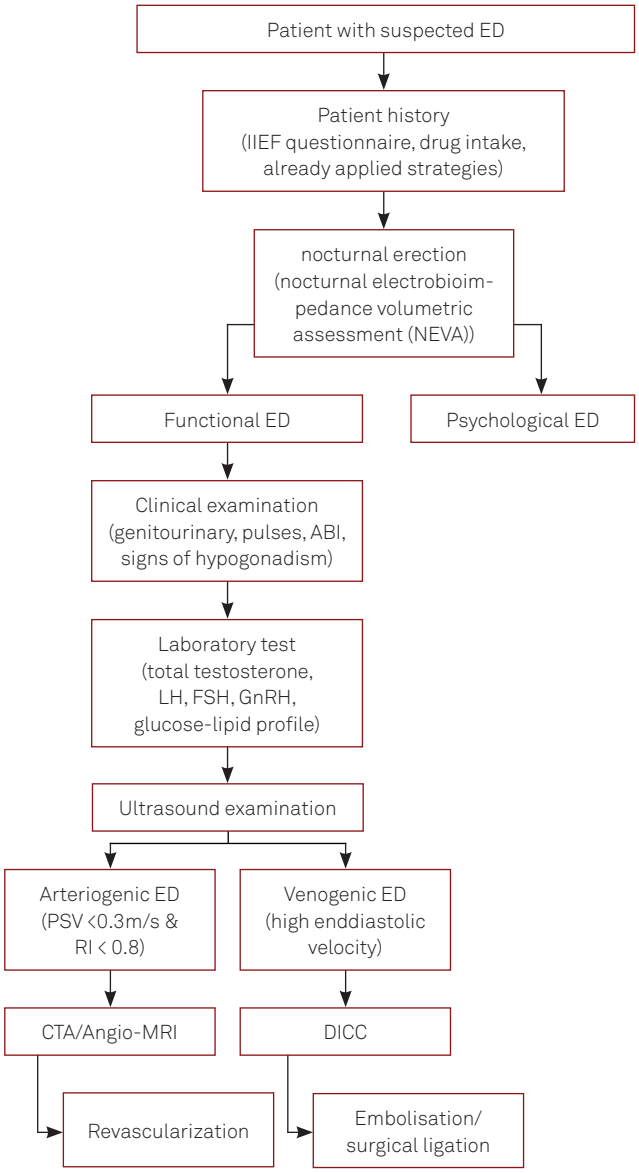

Figure 1. Flow-chart providing an overview on diagnostic and therapeutic approaches in patients with suspected erectile dysfunction.

cularization is suggested as a next step, particularly in patients with macroangiopathic disease (Figure 1). Of note, endovascular revascularization is no option in microangiopathic disease. In general, a CTA is preferred for the following reasons: better availability and time-saving investigation as well as it being the favourable imaging modality for the assessment of calcification (i.e. differentiation of calcified versus soft plaques).

Von Allmen et al. published data on lesion morphology of 26 patients not responsive to PDE-5 inhibitors and thus, suspected to suffer from arteriogenic ED [43]. Arterial lesions were assessed by angiography and classified as macro and microangiopatic. Macroangiopathy was defined as > 70 % stenosis of the main arteries including the internal pudendal artery. Microangiopathy represented small (< 1 mm) arteries distal to the internal pudendal circulation i.e. penile arteries that were rarefied or occluded with a lack of adequate reconstitution. Seventeen macroangiopathic lesions were observed involving the common (n = 2), internal iliac (n = 10), and internal pudendal artery (n = 5) in 11 patients. Microangiopathy was observed in seven patients and the remaining eight patients revealed no arteriopathy. Interestingly, patients presenting with macroangiopathic disease were shown to have a higher prevalence of PAD (63.6 % vs. 6.7 %, p = 0.003).

Usually, a retrograde puncture of the contralateral common femoral artery is performed. After catheterization of the common iliac artery (Figure 2), angiographic imaging of the common, external, and internal arteries is performed. Thereafter, if necessary, the catheter is advanced into the hypogastric artery and pudendal artery for selective angiography. The latter is frequently and successfully engaged with a 0.014 guidewire.

To date, no specific guidance based on clinical studies exist, as to whether stenting is superior to balloon angioplasty in these oftentimes small-calibre arteries. Balloon angioplasty of the pudendal artery was shown to restore blood flow and substantially improve the symptoms of ED during short-term follow-up [44]. However, it is noteworthy that arteriogenic ED is accompanied by a veno-occlusive disorder in up to 80 % of patients [43]. The value of intra-arterial pressure gradient measurements is unclear.

The recently published PERFECT-2 Study [45] evaluated balloon angioplasty for isolated penile artery stenoses (n = 34 lesions) in 22 ED patients. The primary endpoint was in-segment restenosis (≥ 50 %) by CTA at the eight-month follow-up. One year sustained clinical success (IIEF-5 score ≥ 22 or maintaining a ≥ 4 improvement to baseline) was considered as secondary endpoint. Mean lesion length was 11.1 ± 9.0 mm and the mean IIEF-5 score at baseline was 10.3 ± 4.5. Procedural success was 91 %. Restenosis at eight months was observed in 14/34 (41.2 %) lesions (13/22 patients). At one year, the secondary endpoint was achieved in 50 % (11/22) of patients.

Furthermore, the ZEN trial by Rogers et al. evaluated drug-eluting stenting (with Zotaralimus) for the treatment of ED in patients with suboptimal response to PDE-5 inhibitors [42]. Within this prospective trial, a total of 30 patients (45 internal pudendal artery lesions) were treated with drug-eluting stent in a multicentre but single-armed setting. Mean lesion length was 18 mm and procedural success rate was 100 %. During follow-up, no stent fracture was observed. The primary feasibility endpoint, defined as an improvement of IIEF score ≥ 4, was achieved in 59.3 % of patients at the six-month follow-up. Binary restenosis (≥ 50 % lumen compromise by angiography) was reported in 34.4 % at the same interval. Based on these findings, drug-eluting stenting of the pudendal arteries is considered safe and beneficial to the majority of patients. Nevertheless, the rate of non-responders was rather high (40.1 %), which may be attributed to microangiopathy frequently observed in ED patients [43] and to other co-morbidities.

The most common pathophysiological mechanisms of arterial ED is atherosclerosis. Not surprisingly, ED shares the common cardiovascular risk factors [6] as outlined in

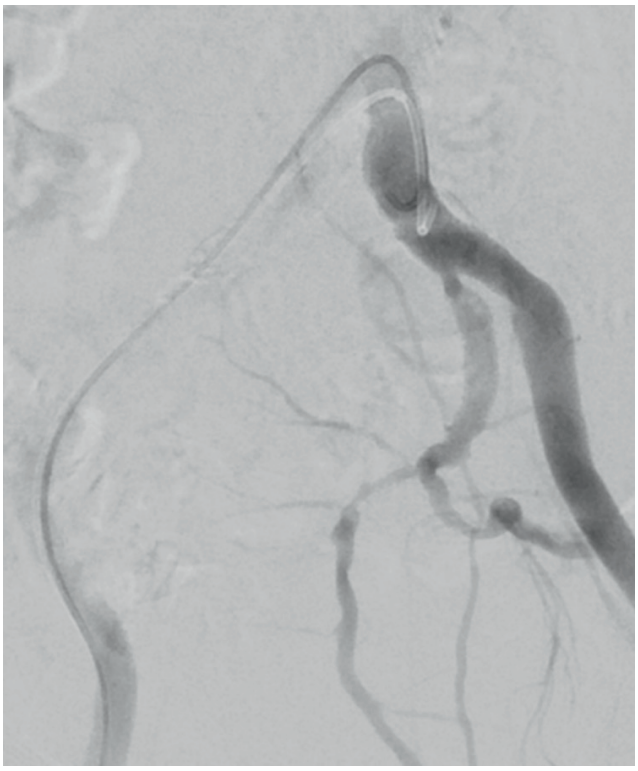

Figure 2. Intraarterial angiogram of the left common iliac and subsequent external and internal iliac arteries after contralateral catheterization via puncture of the right common femoral artery illustrating a moderate (50 %) stenosis of the proximal internal iliac artery.

Table I. Of interest, ED frequently precedes coronary and peripheral artery disease by two to five years (mean three years) [5, 6]. Nevertheless, there is a remaining gap in evidence on routine screening for ED in men. In addition to atherosclerosis, arterial ED may occur iatrogenically in consequence of different reasons for iliac artery occlusion. In some patients, the internal iliac artery may be shuttered i.e. due to the iliac branch in patients undergoing endovascular aortic aneurysm repair. Other men may lose one or even both internal iliac arteries because of arterial embolization for the treatment of aneurysm. Furthermore, there have been controversial postoperative incidences of ED reported after open and endovascular aortic repair [46, 47].

Venous imaging and endovascular therapy of venogenic ED

In patients with suspected veno-occlusive dysfunction (i.e. high end-diastolic velocities), dynamic cavernosometry and cavernosography (DICC) is considered the gold-standard for diagnostics [14]. Dynamic cavernosometry requires the injection of an erection promoting drug to obtain a rigid erection. Thereafter, a fluid is pumped into the penis with known rate and pressure. This allows to obtain information about the pressure within the corpora

Table I. Overview on the common cardiovascular risk factors associated with erectile dysfunction (ED) [6].

Age
Hypercholesterolemia
Hypertension
Insulin-resistance and diabetes mellitus
Smoking
Obesity
Metabolic syndrome
Sedentary lifestyle
Depression

cavernosum during penis erection. For cavernosography, contrast medium is injected to visualize any venous leakage by X-ray screening during penis erection.

In case of venous-occlusive dysfunction, the primary treatment strategy is to cut off venous leakage. Surgical therapy involves ligation of the deep dorsal vein and its collaterals. However, this treatment strategy is invasive, is performed under general anaesthesia and usually requires the patient to stay in the hospital for three days. The long-term success of ligation of the deep dorsal vein and its collaterals is reported to be 25 % [48, 49]. In addition to surgical ligation therapy, endovascular embolization therapy is considered a less invasive option. Aschenbach et al. reported their experience of endovascular embolization in 29 men with ED due to veno-occlusive dysfunction confirmed by DICC [50]. The embolization procedure was performed via transfemoral access using N-butyl-2-cynoacrylate (Histoacryl). No complications were observed and technical success was obtained in 27/29 (93.1 %) of patients. The two failures were attributed to anatomical reasons. Clinical success was achieved in 24/27 (88.8 %) of patients.

The exact prevalence of veno-occlusive disorders in ED patients remains unclear. In general, primary diagnostics are focusing on arterial pathologies. However, arteriogenic ED may be accompanied by a venogenic disorder in up to 80 %. This in addition to microangiopathic disease, other co-medication, and co-morbidities may be the main reason for the rather high rate of non-responding ED patients. In line, a proper patient history and thorough diagnostic approach is mandatory in ED patients.

Conclusions

The prevalence and awareness of ED is increasing for various reasons. In addition to the psychological strains for men and their partners, ED is closely related to cardiovascular diseases. ED shares the common cardiovascular risk factors but moreover, was shown to precede cardiovascular events by about three years. In addition to the arterial

pathophysiologies, ED patients frequently suffer from veno-occlusive disorders.

In consequence, patient history shall incorporate ED for its predictive value as well as to provide men suffering from ED with a proper diagnosis and therapy.

At present, the refinements in endovascular therapy allow for minimal-invasive revascularization of erection-related arteries. Its role in the complex framework of the multifactorial causes of ED requires further scientific scrutiny.

Electroic supplementary material

The electronic supplementary material is available with the online version of the article at http://dx.doi.org/10.1024/0301-1526/a000627.

ESM 1. Questionnaire.
Full Questionnaire: The International Index of Erectile Function (IIEF-15).

ESM 2. Questionnaire.
Abbreviated Questionnaire: The International Index of Erectile Function (IIEF-15).

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