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EDITORIAL COMMENT

Endovascular Treatment for Erectile Dysfunction

An Old Paradigm Revisited*

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In 1962, the science historian Thomas Samuel Kuhn described a *paradigm* as not just current scientific theory, but rather the entire world view that encompassed this knowledge (1). Scientific progress is made when there are anomalies that cannot be explained in one paradigm, leading to a paradigm shift. In some cases, old paradigms are revisited, synergistic with rapid advances in scientific knowledge and innovation. In these cases, there is augmentation of established therapeutic interventions to new avenues; recent examples include percutaneous coronary intervention, endovascular intervention of aortic aneurysms, transcatheter valvular therapy, and endovascular intervention for erectile dysfunction (ED). Fundamental to endovascular therapy, we must first consider the body of literature that establishes the importance for penile arterial insufficiency (PAI) in ED.

Leriche (2) first described this association in 1932 in a patient with bilateral aorto-iliac disease and ED. However, this association remained unexplored until 1978, when 30 males with ED underwent translumbar aortography followed by puncture of the dorsal artery of the penis, demonstrating severe arterial stenosis or occlusion to the corporal bodies (3). Since then, 10 studies have assessed

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penile arterial blood flow in 629 patients with ED (4–14). Collectively, these studies showed that the incidence of PAI ranges between 37% and 79%, with an average incidence of 76%. These observations established the association between PAI and ED and framed arterial reconstruction or intervention as a possible therapeutic option. Initially, microsurgical reconstruction of penial arterial circulation was attempted from 1973 through 2004 using a number of arterial conduits with a variable extent of penile venous reconstruction (15). Altogether, 31 studies were performed; however, only 4 reports for a total of 50 patients have been considered of adequate quality by the American Urological Association (15). Even these 4 studies were limited by inadequate study design, lack of long-term follow-up, a wide range of complications, and heterogenous surgical approaches. Most importantly, none of these studies were performed for atherosclerotic PAI, but rather for focal stenosis resulting from blunt trauma. However, because of these findings, the American Urological Association considers vascular reconstructive approaches for ED experimental and has advised against it.

Given these surgical limitations, transluminal angioplasty (without stenting) was attempted in the 1980s and 1990s, treating a total of 65 patients with a mean success rate of 55% (Table 1) (16–21). The overwhelming majority of the endovascular interventions (95%, n = 62) were to larger iliac arteries, with only 3 internal pudendal artery (IPA) interventions. In addition, none of the studies had any noninvasive methods of documenting PAI before or after intervention. Similarly, venous insufficiency, an important mechanism for ED, was not assessed. Given the limitations of study design, patient selection, and endovascular techniques used in these studies, the role of endovascular intervention in ED has remained unclear and is rarely considered, unless for treatment of proximal iliac disease in the setting of peripheral artery disease.

Given recent endovascular advances, Rogers et al. (22), in this issue of the *Journal*, conducted a seminal first-in-man prospective, multicenter, single-arm safety and feasibility trial of the zotarolimus-eluting stent implantation in focal atherosclerotic lesions of the IPA among men with ED with suboptimal responses to phosphodiesterase-5 inhibitors. A total of 383 men were screened using stringent clinical, angiographic, and duplex ultrasonographic criteria. Of the 89 patients who underwent pelvic angiography, 67% (n = 60) had severe IPA stenosis, but of those, only 33.7% (n = 30) had suitable anatomic features amenable to intervention. The location of atherosclerosis in the IPA was distal (53.3%), followed by proximal or ostial segments (24.4%), and the mean lesion length was 17.6 ± 99 mm. Forty-five lesions were treated with stents, and technical success was achieved in all patients with no post procedural death or perineal gangrene at 30 days through follow-up (primary safety endpoint). The angiographic percent stenosis pre-procedure was 63.3%, and this reduced to 23.3% post-procedure, but increased again to 41.4% at 6 months. In addition, there was a nonsignificant increase in peak systolic velocity from 14.4 ± 10.7 cm/s to 22.5 ± 23.7 cm/s at 6 months in conjunction with binary restenosis of 34.4% (n = 11). Despite the moderate improvement in peak velocity and significant restenosis rate, in the intention-to-treat analysis, the primary feasibility endpoint (improvement in erectile function from pre-procedure International

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Table 1 Endovascular Treatment of Erectile Dysfunction

First Author, Year (Ref.#)	No.	Angiographic Stenosis	Follow-up (months)	Success Rate (%)
Castaneda-Zuniga et al. 1982 (16)	2	ILA	18	100
Van Unnik and Marsman, 1984 (17)	1	ELA	N/A	100
Goldwasser et al., 1985 (18)	1	ILA	N/A	100
Dewar et al., 1985 (19)	30	70% aorto-iliac, 47% ILA	N/A	33
Angelini et al., 1985 (20)	5	ILA	2 to 18	80
*Urigo et al., 1994 (21)	23	ILA, IPA	N/A	65, 100

*In this study, 65% of patients with internal iliac artery stenosis had improvement in erectile function, whereas all patients with pudendal artery disease had success.

ELA = external iliac artery; ILA = internal iliac artery; IPA = internal pudendal artery; N/A = not available; PTA = percutaneous transluminal balloon angioplasty.

Index of Erectile Function (IIEF-6) score by 4 points or more in more than 50% of subjects) at 3 and 6 months was achieved by 59.3% of patients (95% confidence interval: 38.8 to 77.6).

This study presents the first major step in the application of endovascular intervention and provides several insights for the potential treatment of ED. Of the 383 subjects screened, only 89 (23%) qualified for angiography, and of those, only 30 (7.8%) qualified for the intervention, highlighting the need for appropriate patient selection. Even more importantly, approximately 30% of subjects that met the peak systolic velocity and other inclusion criteria had minimal to normal angiographic appearance, emphasizing the need for more robust, noninvasive screening tools such as computed tomography or magnetic resonance imaging. Furthermore, PAI is a diffuse process, similar to that seen in patients with critical limb ischemia, and discrete lesions are seen in only one third of patients. Therefore, stents alone may not be the best answer for all patients. The procedure, however, seems to be feasible and safe, but there is a high degree of anatomic variability requiring significant operator experience.

The main limitation of this study is the lack of a control arm. In addition, the post-procedure peak systolic velocity, an indication that blood flow improved, did not reach statistical significance. Furthermore, despite a 34.4% binary restenosis rate, efficacy remained at 59.4% at 6 months; hence, the long-term durability of endovascular therapy is unknown. Collectively, these limitations and findings raise concern about the placebo effect. This is supported by a 22% improvement in erectile function in patients receiving placebo in studies evaluating oral phosphodiesterase-5 inhibitors (23). Moreover, the primary feasibility endpoint was selected based on prior studies of oral agents to improve ED; however, given the risk and cost, it is not clear whether this endpoint is appropriate for invasive procedures.

Despite the limitations outlined above, the current study sets the stage for advancing this important field further. Erectile dysfunction is a vascular disease, and a team of experts (urology, cardiology, and primary care) at each center should work collectively to identify, evaluate, and treat these patients. The presence of atherosclerotic lesions in the pelvis does not necessarily result in ED. Unfortunately, the Incidence of Male Pudendal Artery Stenosis in Suboptimal Erections (IMPASSE) study, which was designed to better understand this association, recently was terminated.

At present, endovascular therapy for ED remains investigational; however, given the prevalence of ED and its psychosocial impact, an appropriately powered randomized clinical trial to evaluate this approach clearly is needed. Before doing so, this field is in desperate need of a reproducible and easily performed noninvasive diagnostic tool that can identify PAI and exclude venous leak accurately for proper patient selection and to avoid unnecessary procedures. Only then can this paradigm be revisited.

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Key Words: endovascular treament ■ erectile dysfunction ■ internal pudendal artery ■ penile arterial insufficiency.