Prostate Artery Embolization: Indication, Technique and Clinical Results
Prostataarterienembolisation: Indikation, Technik und klinische Ergebnisse

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ABSTRACT

Background Prostate artery embolization (PAE) is a new embolization therapy to treat benign prostate syndrome (BPS).

Materials and Methods This review article presents the rationale and impact mechanism of PAE, criteria for patient selection, and discusses the anatomy of prostate arteries. The study results are seen in the context of complications and clinical partners.

Results Important preconditions for successful prostate artery embolization are a strict indication, precise knowledge of the anatomy of the pelvic arteries and advanced interventional-radiological skills. Several studies showed that urological parameters after prostate artery embolization improve at a similar level as for established post-surgical treatments. At the same time, it could be proven that prostate artery embolization has no impact on erectile function and is associated with a relatively low complication rate.

Conclusion PAE is increasingly developing to an alternative for the established surgical treatments in BPS patients.

Key Points
▪ PAE is a new embolization method for treating BPS and represents an alternative to classic urological surgical procedure such as TURP.
▪ Due to the low caliber of the prostate artery (0.5 – 2 mm), the presence of anatomical variations, and the arteriosclerosis seen in most older men, PAE is a technically challenging embolization method.
▪ In patients with a high postoperative bleeding risk in classic urological surgical treatment concepts, PAE is a very gentle alternative method.

Citation Format

ZUSAMMENFASSUNG

Hintergrund Die Prostataarterienembolisation (PAE) ist ein junges Embolisationsverfahren zur Behandlung des benignen Prostatasyndroms (BPS).

Material und Methode In dieser Übersichtsarbeit werden die Rationale und Wirkungsmechanismen der PAE vorgestellt und die Patientenauswahl sowie die Anatomie der Prostataarterien diskutiert. Die Studienergebnisse werden im Kontext von klinischen Ansprechraten und Komplikationen betrachtet.

Introduction

Prostate artery embolization (PAE) is a new embolization method for treating benign prostate syndrome (BPS) which was first presented in 2010 in two interventional-radiological case descriptions [1]. It was basically a “proof-of-principle” that directed the interest not only of the interventional radiologists, but also the affected patients towards this minimally invasive method.

BPS – etiology, clinical picture, treatment with medication and surgical treatment

Typical symptoms for benign prostate syndrome (BPS) include lower urinary tract syndroms (LUTS) and bladder outlet obstruction (BOO) [2]. Bladder outlet obstruction is caused by a benign enlargement of the prostate (benign prostate hyperplasia – BPH). Strictly speaking, BPH is a histological diagnosis associated with proliferation of stromal and epithelial cells [2, 3]. The greater proliferation of stromal and epithelial cells in combination with the decreased programmed cell death results in both fibroadenomas and an increase in gland tissue [2, 3]. This cell proliferation is regulated by androgens, estrogens, and growth factors. The most important androgen is testosterone which is almost fully converted in the prostate by type II 5α-reductase into biologically active dihydrotestosterone (DHT) [4]. Type II 5α-reductase also plays an important role in the development of hyperplasia [4, 5].

Prostate size and symptoms are not necessarily correlated. The symptoms of BPS can be classified as obstructive symptoms (emptying phase) and irritative micturition syndrome (storage phase) [2]. The symptoms of the emptying phase include delayed start of micturition, prolonged micturition time, weakening of the voluntary urge to urinate and dysuria are symptoms of the storage phase [2].

The indication for BPS treatment is determined based on the symptoms and the effect on quality of life. BPS is basically treated with α1-adrenergic receptor antagonists (e.g. tamsulosin, alfuzosin) which relax the smooth muscles of the bladder neck, which is most fully converted in the prostate by type II 5α-reductase into biologically active dihydrotestosterone (DHT) [4]. Type II 5α-reductase also plays an important role in the development of hyperplasia [4, 5].

Rationale/impact mechanisms of PAE

The effect of PAE is based on multiple impact mechanisms. Embolization causes displacement of intraprostatic vessels and pre-capillary arterioles, resulting in irreversible ischemia. An inflammatory response and the formation of edema then result in ideally complete anoxia. The shrinking process begins after absorption of the edema components and scar formation. At the same time the level of intraprostatic testosterone and of converted highly biochemically active dihydrotestosterone (DHT) decrease. Both effects lead to the shrinkage of the prostate [6]. The administration of the adequate particle size is essential to support shrinkage. A deep penetration and a too proximal embolization increase the risk for urethral necrosis. By destroying the intraprostatic nerve ends, successful embolization results in a reduction of the α1-adrenergic receptor density causing relaxation of the smooth muscle fibers [7]. In BPH, the density of the α1-adrenergic receptors is approx. 6-times higher than in the normal prostate and induces the relaxation of smooth muscle cell tonus within the bladder neck affecting the flow from the bladder into the urethra. The receptor expression drops significantly after embolization resulting in a decrease in muscle tone. This may explain the reported early clinical successes after PAE, also due to the notable reduction in prostate volume [9, 10].

Patient selection

Important diagnostic predictors for symptomatic BPS are age (≥60 years), urodynamical examinations including maximum urine stream (Qmax, uroflowmetry), postvoided residual volume (PVR) and the determination of the prostate volume via transrectal ultrasound (TRUS). The severity of the patient’s symptoms caused by BPH can be best determined using the International Prostate Symptom Score (IPSS) questionnaire, which includes 7 questions regarding BPH symptoms. In addition, the IPSS questionnaire includes one question regarding quality of life (Qol). Symptoms are rated on a scale of 0 to 5 points (0 = no symptoms and 5 = severe symptoms). The maximum total number of points is 35. Based on this self-evaluation by the patient, a total point value <8 corresponds to minimal symptoms, 8 – 19 to moderate symptoms, and 20 – 35 to severe symptoms. The PSA value must be evaluated with respect to the risk of prostate cancer since BPH can result in an increase in the PSA value. In case of suspicion of
renal insufficiency due to a blockage, the serum creatinine must also be taken into consideration to evaluate BPH. Therefore, collaboration with urology is essential for determining the indication for PAE. The requirements for PAE are summarized in Table 1 and the contraindications in Table 2.

Under consideration of the fact that symptomatic BPH usually occurs in the 6th to 7th decade of life in men, patients often also have comorbidities so that urological surgical methods are associated with an increased risk. The postoperative bleeding risk must be mentioned here in particular [11]. There is a very high postoperative bleeding risk in the case of classic urological surgical treatment concepts in patients undergoing continuous anticoagulation therapy such as dual antiplatelet therapy or phenprocoumon (Marcumar®) after stroke or heart attack or in patients with cardiovascular implants. PAE is an alternative to TURP and open enucleation of the prostate even in patients with a prostate volume > 65 ml since the complication rate of urological surgical procedures with urogenital infections and postoperative bleeding increases greatly in the case of larger prostate volumes. Particularly younger, sexually active patients fear retrograde ejaculation, which can be a normal consequence of TURP in over 75% of patients. Erectile dysfunction following surgery, which is frequently mentioned as a complication, is rarer (0.5–1%). There is also a fear of urinary incontinence so that PAE is a good alternative to standard surgical procedures in this patient group. In our many years of experience with PAE, we have worked in close collaboration with urology to determine indications for which PAE is now our first-choice treatment method (Table 3).

Technique

PAE is performed under local anesthesia at the inguinal puncture site. Additional intravenous pain medication is usually not necessary. A urinary catheter should be inserted. The catheter is used for orientation during PAE and also makes the intervention significantly easier for the patient by allowing unobstructed urine flow.

The standardized PAE method as practiced by us in interventional radiology is described step-by-step in the following. The first step is retrograde puncture of the right common femoral artery and insertion of a short 5F catheter. As a rule, bilateral embolization of the prostate arteries is targeted. To identify the anatomical vascular conditions and in particular the origin of the prostate arteries on both sides, it is recommended to acquire an arterial rotation CT angiography scan (cone-beam CT). A pigtail or RIM angiography catheter is first inserted via the introducer. The catheter tip should be positioned above the bifurcation of the common iliac artery in the distal abdominal aorta since even an atypical origin of the prostate artery can be reliably detected in this position (Fig. 1). The rotation CT angiography scan of the pelvic arteries was acquired with a total of 90 ml of a contrast agent/Na-Cl mixture (60%/40%), an injection rate of 8 ml/s, and an X-ray delay of 7 s using pre-warmed contrast agent with an iodine concentration of 250 mg/ml. The internal iliac arteries and their branches can be fully visualized on both sides on a rotation angiography scan with a total detector width of 30–40 cm. If this is not technically feasible, rotation CT angiography can be performed by positioning the guide catheter in the left and right internal iliac arteries separately for each side. The side on which the intervention is started does not affect treatment success. We routinely begin with probing of the left internal iliac artery with a 4F RIM catheter (e.g. Merit Medical, Salt Lake City, USA) as the guide catheter. Alternatively, a 5F “Roberts Uterine” catheter (e.g. Cook, Bloomington, IN), a 5F Sidewinder catheter or a “Pisco Prostatic” catheter developed specifically for PAE (e.g. Merit Medical, Salt Lake City, USA) can be used. However, it must be taken into consideration that both of these alternative probe catheters must first be configured for the intended purpose via the pelvic axis which requires a cross-over maneuver. If the cross-over maneuver is not successful, a second access can be alternatively created on the contralateral side to again attempt to probe the ipsilateral internal iliac artery.

Using and comparing the 3D reconstruction as maximum intensity projections (MIP) of the rotation CT angiography scan, the origin of the prostate artery is identified and the optimum angiulation for later probing is determined (Fig. 2, 3). Alternatively,
manual overview angiography with ipsilateral alignment of the detector of 30–40° oblique and caudocranial angulation of 10–15° can be performed to identify the prostate artery (Fig. 4). A microcatheter is then inserted using the coaxial technique. We use the 2.7F Progreat α (Terumo, Tokyo, Japan) catheter as the standard microcatheter. Alternatively, a 2.0F Progreat α (Terumo, Tokyo, Japan) with a 0.014 inch Cirrus guide wire (Cook, Bloomington, IN, USA) can be used. The prostate artery has an average diameter of 0.9 mm (range: 0.5–1.5 mm) and usually originates from the internal pudendal artery or from a common origin with the superior vesical artery [12,13]. The exact anatomical conditions and vessel variations are explained in greater detail below.

The prostate artery must be superselectively probed with the microcatheter. The prostate is typically supplied from one side by only one main branch of the prostate artery. Directly in front of the prostate, the prostate artery divides into a cranial branch for supplying the central gland parts and a lateral branch for supplying the peripheral zone (Fig. 5). It should be taken into consideration that the urethral and capsular branches must also be embolized. Embolization of the inferior vesical artery with branches to the seminal vesicles and bladder wall should be avoided.

Deviating from the frequently quoted embolization with microspheres with 150–250 µm polyvinyl alcohol (PVA) particles (Cook, Bloomington, IN, USA) with a size of 300–500 µm (Embospheres 300–500 µm, Merit Medical, Salt Lake City, USA) [11] or the embolization technique with multiple catheter positions (PERFeCTED method) [14], we prefer a technique with a catheter position with small biocompatible 250 µm Embosphere Microspheres (Boston Scientifics, Natick, MA, USA). The Embosphere Microspheres are combined in a precisely defined ratio depending on the contrast agent being used so that the microspheres remain in suspension as long as possible and sedimentation does not occur. For complete unilateral embolization of the prostate artery, fewer than 0.5 ml of microspheres are generally needed (more in a mixture with contrast agent). The end goal of embolization is reached upon “flow stop” of the microspheres/contrast agent mixture. Reflux should be avoided. To test the success of the procedure, the microcatheter is retracted slightly into the prostate artery and a control angiography scan is performed via manual injection of 1 ml of contrast agent. This angiography scan should be performed slowly and with the least amount of pressure possible (manual injection rate approx. 0.2 ml/s). After completion of embolization on the contralateral side, the microcatheter is removed and the ipsilateral internal iliac artery is probed with the RIM catheter. PAE is then repeated on the ipsilateral side in the same manner as previously described. The embolization procedure is very short in our preferred embolization technique. However, probing of the prostate artery can be very time-consuming depending on the anatomical vessel variations with elongated iliac arteries and arteriosclerotic vessels with kinking or stenosis at the origin of the prostate artery (Fig. 6). It must be taken into consideration...
that fluoroscopy times can exceed 60 minutes in individual cases, particularly in the establishment phase of PAE. However, we have found that fluoroscopy times decrease with an increase in experience.

Anatomy of prostate arteries

Based on anatomical textbooks with visualization of the origins of the individual branches from the internal iliac artery, the German mnemonic used in anatomy lessons for the vessel branches of the internal iliac artery of the female pelvis can also be applied to the male pelvis (“Ingo suss Glut-glühend oben, um sich Blase, Prostata und Rektum zu pudern”) (▶Table 4). Accordingly, the prostate artery typically originates as the 9th branch together with the superior vesical artery from the internal iliac artery. The prostate artery then runs obliquely in a caudal direction and reaches the prostate under the bladder anteromedially. Over its course, there are typically branches to the seminal vesicles and also the base of the bladder especially since a common origin of the superior and inferior vesical artery and the prostate artery is routinely seen. The anatomical conditions of the arterial branches from the internal iliac artery are schematically shown in ▶Fig. 7. However, this is a highly idealized representation. Bilhim et al. analyzed anatomical variations in 75 PAE patients based on angio-CT and the angiography scan performed immediately prior to PAE [15]. The most common origin of the prostate artery was seen in the middle third of the internal pudendal artery in 34 % of cases (▶Fig. 2). A common origin of the prostate artery and the superior vesical artery was observed in only 20 % of cases (▶Fig. 6). However, it must be taken into consideration that the currently available analyses and experience are based on only a relatively small number of patients. Thus, the mnemonic provides only basic orientation for locating the prostate artery. An important observation is also
that two independent prostate arteries were observed per pelvis side in 43% of cases [15]. On average, 2.9 ± 0.9 prostate arteries per patient were identified in the small collective. In our experience, small anastomoses or collateral vessels from the prostate artery to the medial rectal artery, internal pudendal artery, or inferior vesical artery can be identified in approx. one third of all patients (▶ Fig. 8). Depending on the extent, either a slightly more distal catheter position or larger microspheres should be selected for embolization. In the case of pronounced anastomoses, e.g. to the posterior bladder wall, we use 400 µm instead of 250 µm microspheres. Anastomoses to the opposite side of the prostate are also observed in 20% of all patients (▶ Fig. 9). This also seems to be a reason for the clinical success of unilateral PAE in many cases [11].

Patient management
The night before or morning of the intervention, our patients receive a single dose of an antibiotic (e.g. 500 mg of ciprofloxacin po) in combination with a non-steroidal antiinflammatory agent in an antiphlogistic concentration (e.g. 800 mg of ibuprofen po) and 40 mg of omeprazole po as premedication. If a patient does not tolerate iodine-containing contrast agents, premedication is administered at the ward. In general, patients do not experience pain during or after PAE. 40 drops of Novalgin® (metamizole) can be administered as needed in the case of postembolization syndrome or 2 × 1 tablet 10/5 mg of Targin® extended release (oxycodeone + naloxone) po in the case of significant pain. 1 mg of granisetron in 100 ml of isotonic NaCL as a short i. v. infusion or 3 × 30 drops of metoclopramide can be administered in the case of nausea and vomiting. After the intervention, antibiotic and antiphlogistic therapy should be continued for an additional 10 days (e.g. 2 × daily 250 mg of ciprofloxacin + 800 mg of ibuprofen + 40 mg of omeprazole). Shrinkage starts approximately 1 month after embo-
Since the effect of decreased tone of the smooth muscles is insufficient in some patients, we recommend continuing BPS medication for one month. This medication can then be discontinued in coordination with the treating urologist. During the informed consent discussion, patients should be explicitly informed of the newness of the method and the lack of long-term results. For this reason, patients should ideally be examined and treated under study conditions. In our opinion, this also includes follow-up of the patient after 1, 3, 6 and 12 months with recording of the IPSS, QoL, IIEF, Qmax, postvoid residual volume, prostate volume, and any side effects.

**Study results**

750 patients from 13 studies with a follow-up period of 3 – 12 months were further evaluated in a current metaanalysis [16]. A significant improvement in the observed endpoints compared to the baseline values was seen in these patients [16]. In detail, the IPSS improved by –12.8 points, the QoL by –2.3 points, the maximum urine flow (Q_{max}) by 5.3 ml/s, the prostate volume by –29.8 ml, postvoid residual volume by –66.9 ml, the International Index for Erectile Function (IIEF) by 1.3 points and the PSA value by –0.8 ng/ml. This corresponded to an improvement among study patients of 31 – 85 % for IPSS, 29 – 81 % for QoL, 17 – 132 % for Qmax, 5 – 45 % for prostate volume, 35 – 76 % for postvoid residual volume and 0 – 18 % for IIEF [16].

To date, data from 3 comparative studies with a total of 297 patients has been published (149 patients in the PAE group and 148 patients in the control group TURP or open adenomectomy) [17 – 19]. These data were able to show that the length of hospital stay in the PAE group was shorter than in the control group (median 2.5 days vs. 4.8 days) however with a slightly longer intervention time (90 min vs. 62 min) [16]. The largest comparative study with a total of 114 patients (randomization ratio 1:1) did not show a statistically significant difference between the values for IPSS, QoL, Q_{max}, and postvoid residual volume 6 months after PAE or TURP [17]. According to the study register “clinicaltrial.gov”, an additional 3 clinical studies (NCT01789840, NCT01789840, ...
NCT02054013, NCT02566551) comparing PAE vs. TURP are currently active. One study is a non-randomized multicenter study while the other two studies are controlled randomized single-center studies. Moreover, a controlled randomized single-center study is recruiting patients for the comparison PAE vs. placebo and a further controlled randomized multi-center study is recruiting patients for the comparison PAE vs. medication. For this reason, additional study data regarding the efficacy of PAE can certainly soon be expected. Only non-randomized single-center observational studies or retrospective case cohorts examining which particles and which particle size should be used and what effect the volume of the prostate, the patient’s age, and the unilateral or bilateral embolization have on the success of PAE are available. It was able to be that spherical polyvinyl alcohol particles (sPVA) and non-spherical polyvinyl alcohol particles (nsPVA) are equally effective for prostate artery embolization [20]. With respect to the particle size being used, 100 µm nsPVA compared to 200 µm nsPVA yielded a greater reduction of the prostate volume and the PSA value, while 200 µm nsPVA was associated with a higher clinical success rate [21]. sPVA size did not affect the relapse rate after 12 months [22]. Prostate volume does not seem to have an effect on the outcome of PAE since there is no statistically significant differences for IPSS, QoL, and IIEF 6 months after treatment between the groups PV < 50 ml, PV 50 – 80 ml and PV > 80 ml [23]. In contrast, a younger age (<65 years) and the bilateral embolization of the prostate arteries seem to be associated with improved clinical success [20].

Complications

PAE is a very safe method under the condition that it is performed as a superselective embolization method for the prostate artery. To date, only one case of accidental embolization of the posterior bladder wall in a series of 89 patients resulting in ischemia with bleeding and consecutive partial resection of the bladder wall has been reported in the literature [11]. However, except for possible misembolization, no major complications are to be expected. Therefore, it is even more important that the catheter position is checked ideally from two planes on angiography via the microcatheter immediately prior to embolization. The position of the prostate can be determined with the help of a bladder catheter blocked with contrast agent. In addition, comparison with a current prostate MRI examination should be performed prior to embolization. This double examination virtually rules out misembolization.

Typical complications of the endovascular embolization intervention are primarily minor. Compared to UAE, the pain experienced in PAE is negligible. In our experience which is in accordance with the literature, some patients report a feeling of slight pressure or minimal pain in the pelvic region radiating into the perineal region in the first two days after PAE. However, these issues can be well managed with oral analgesics. The large majority of patients are completely symptom-free after PAE. A few patients can experience blood or coagulum in their ejaculate up to approx. one month after PAE as a possible late complication. This is usually an embolization effect due to the initial stages of necrosis of the prostate and does not have clinical significance. However, this complication can also rarely be the result of misembolization of the seminal vesicles. In the literature acute urinary retention is a common complication seen in 9.4 % of cases (14/149) [18]. In our own patients, we have not observed this complication since the perinterventional administration of non-steroidal antirheumatic drugs in an antiphlogistic dose. Further minor complications of PAE described in the literature in descending order of frequency are post-embolization syndrome (4 %), hematuria (3.4 %), urinary tract infections (2.7 %), increase in urge symptoms (2.0 %), hematospermia (0.7 %), transient rectal bleeding (0.7 %), transient ischemia of the pubic bone (0.7 %), and transient pelvic pain (0.7 %) [16, 24].

Conflict of Interest

The authors declare that they have no conflict of interest.

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