Diagn Interv Radiol 2019; 25:134–143

INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

The value of contrast-enhanced ultrasonography in detection of prostatic infarction after prostatic artery embolization for the treatment of symptomatic benign prostatic hyperplasia

Hippocrates Moschouris
Konstantinos Stamatiou
Katerina Malagari
Kyriaki Marmaridou
Konstantinos Kladis-Kalentzis
Michail Kiltenis
Nikolaos Papadogeorgopoulos
Aikaterini Tsavari
Kassiani Manoloudaki

PURPOSE

We aimed to assess the clinical and predictive role of contrast-enhanced ultrasonography (CEUS) as the primary method for imaging evaluation of prostatic artery embolization (PAE) for the treatment of symptomatic benign prostatic hyperplasia (BPH).

METHODS

Thirty-one patients with symptomatic BPH, treated with PAE from October 2016 until February 2018, were enrolled in this prospective, single-center study. Microspheres (100–700 μm) were utilized for PAE. International prostate symptom score (IPSS), quality of life (QoL), maximum urinary flow (Qmax), prostatic volume (PV) and post void residual volume (PVR) were measured at baseline and at 1, 3, and 6 months post PAE. Unenhanced transabdominal US was utilized for PV and PVR measurements; prostatic enhancement was studied with transabdominal CEUS at baseline, during the procedure, 1 day and 1, 3, and 6 months post PAE. Technical success was defined as embolization of the PA of at least one pelvic side. Clinical success was based on the improvement of IPSS and QoL, with no need for any additional treatment. Follow-up time ranged from 6 to 18 months (mean, 9.7±4.3 months). Clinical success rates were calculated and changes in prostatic enhancement were correlated with the outcome parameters.

RESULTS

Technical success rate was 90.3%. Clinical success rates at 3, 6, and 12 months post PAE were 85.7%, 85.7%, and 79.1% respectively. Improvement of outcome parameters (baseline vs. 6-month values) was statistically significant, with 12.4 points mean reduction of IPSS (50.4%, $P = 0.003$), 2.0 points mean reduction of QoL (45.4%, $P < 0.001$), 30.3 mL mean reduction of PV (30.2%, $P < 0.001$), 72.6 mL mean reduction of PVR (51.8%, $P = 0.005$) and 8.6 mL/s mean increase in Qmax (103%, $P = 0.002$). The most significant complications were bladder ischemia (n=1), and ischemic rectal ulcer (n=1), both attributable to nontarget embolization, with complete recovery. CEUS 1 day post PAE demonstrated prostatic infarcts in 26/28 (92.8%) patients. The percentage of prostatic infarction (pPI, defined as prostatic infarcted volume 1 day post PAE divided by baseline PV) was 1%–71%. There was a very strong positive correlation between pPI and prostate shrinkage (r=0.81, $P < 0.001$), but a weak correlation between pPI and the improvement of the other outcome parameters (r= 0.01–0.36; $P = 0.093$–0.965). However, in the subgroup of patients with indwelling bladder catheter (9/28 patients), successful removal of the catheter was achieved only in patients with pPI>10%.

CONCLUSION

CEUS appears to be a practical method for the study of the local ischemic effect of PAE, with potential predictive value.

From the Departments of Radiology (H.M. ✉ *hipmosch@gmail.com*, K. Marmaridou, K.K.K., M.K., N.P.), Urology (K.S.) and Pathology (K. Manoloudaki, A.T.), Tzaneion General Hospital, Piraeus, Greece; Department of Radiology (K. Malagari), Athens University, Attikon Hospital, Chaidari, Athens, Greece.

Received 7 September 2018; revision requested 16 October 2018; last revision received 12 December 2018; accepted 24 December 2018.

DOI 10.5152/dir.2019.18410

More than 40 years after its original application for the control of prostatic hemorrhage (1), prostatic artery embolization (PAE) is becoming increasingly popular as a minimally invasive modality for the treatment of symptomatic benign prostatic hyperplasia (BPH). Although the mechanisms of action of PAE are not fully understood, the short-and intermediate-term results indicate substantial improvement of the clinical parameters routinely used to quantify the lower urinary tract symptoms associated with BPH; the clinical efficacy of PAE is combined with a low rate of usually minor complications (2–4). PAE appears to be particularly beneficial for elderly, unfit for surgery patients with

You may cite this article as: Moschouris H, Stamatiou K, Malagari K, et al. The value of contrast-enhanced ultrasonography in detection of prostatic infarction after prostatic artery embolization for the treatment of symptomatic benign prostatic hyperplasia. Diagn Interv Radiol 2019; 25:134–143.

medically resistant, symptomatic BPH, but has also been utilized for the management of the same symptoms in younger patients who do not accept the invasiveness and risks of the standard urological operations for BPH (5).

Prostatic ischemia plays a pivotal role in the therapeutic mechanisms of PAE (6). At present, detection of prostatic infarcts by means of contrast-enhanced magnetic resonance imaging (CEMRI) is the standard approach for the study of PAE-induced ischemia (7–10). Prostatic infarcts are readily demonstrated as enhancement defects on CEMRI post PAE and volumetric techniques can accurately assess the proportion of the infarcted prostatic tissue. The latter correlates with 24-hour post-PAE prostate-specific antigen (PSA) values and with prostate volume reduction (8); CEMRI-detected prostatic infarction is also considered a potential predictor of clinical success (7, 8). Additionally, thanks to the high soft-tissue contrast resolution of MRI, the effect of PAE on the different prostatic zones has been demonstrated (10), and a good response of adenomatous dominant BPH to PAE has been highlighted (9). However, cost and availability issues can limit the application of CEMRI post PAE, particularly if serial studies have to be performed on large groups of patients. First day (or even immediate) post-PAE evaluation is usually not performed with MRI and the potential value of such an early imaging feedback has been underscored (8). Contrast-enhanced ultrasonography (CEUS) is another option for dynamic abdominal imaging and has also been proved effective for the differentiation of the viable (enhanced) from the infarcted (nonenhanced) tissue; therefore, CEUS is considered a valid complementary modality for the study of tumor infarction, during and after therapeutic embolization (11). Compared with CEMRI, CEUS could be more cost-effective and (at least in some centers) more readily available. Early reports on utilization of CEUS post PAE have confirmed the feasibility of CEUS and its ability to delineate prostatic infarcts; however, only small groups of patients have been studied and evidence regarding the clinical relevance of the CEUS findings is at present very limited (12, 13).

The main purpose of our study was to systematically evaluate CEUS as the primary technique for postprocedural imaging of PAE and to assess the role of CEUS-detected prostatic ischemia after PAE as predictor of clinical outcome.

Main points

- Prostatic artery embolization (PAE) is often technically demanding and time-consuming but is also associated with high rates of clinical success (short term success, 79.1%–85.7% in this study) and usually minor complications.
- The modes of therapeutic action of PAE are not fully understood, but they are at least partially associated with prostatic ischemia and subsequent shrinkage.
- Contrast-enhanced ultrasonography (CEUS) appears to be an attractive modality for the study of prostatic ischemia (infarction) induced by PAE, and CEUS findings have potential predictive value.

Methods

Patients

We conducted a prospective, single-center, single arm study of 31 male patients who were treated with PAE for symptomatic BPH in our institution from October 2016 until February 2018. In line with the majority of other PAE studies (3), inclusion criteria were: age >50 years; moderate-to-severe lower urinary tract symptoms (International Prostate Symptom Score, IPSS >18); failure of medical treatment (at least 6 months of administration of 5α-reductase inhibitors or selective α1 blockers) or urinary retention managed with indwelling bladder catheter (IBC), with at least three failed attempts of catheter removal prior to PAE; prostate with a sonographically calculated volume of more than 35 mL. Exclusion criteria were previous surgical or interventional prostate treatments, urinary tract infection, prostate or bladder cancer, neurogenic bladder, large (>3 cm) bladder diverticula or bladder stones, contraindications to angiographic procedures, and vascular pathologies which precluded safe arterial access.

Prior to PAE, the patients were clinically evaluated by the urology service, and uroflowmetry was performed to measure the maximum urinary flow rate (Qmax). The severity of their symptoms was quantified by means of IPSS, and quality of life (QoL) questionnaires. Patients with IBCs were excluded from baseline uroflowmetric and IPSS measurements. Serum PSA was also measured; patients with PSA ≥4 ng/mL (n=6, with PSA ranging from 7.2 to 13.1 ng/mL) were further investigated by US-guided prostate biopsy and prostate cancer was excluded. In this study PSA was not utilized to assess the effectiveness of PAE.

Before PAE, the interventional radiologists and the referring urologist informed the patients on technical and clinical aspects of the procedure, on the benefits and potential complications, and on other treatment options, and written informed consent was obtained from all patients. The institutional review board approved the study. A subgroup of the studied patients had been included in previous work (12, 13).

Preprocedural imaging

Since a cone-beam computed tomography (CT) facility was not available during the period of the study, pelvic CT-angiography (CTA) was performed with a 64-row scanner (Optima CT 660, GE Healthcare) in all patients prior to intervention, to study arterial anatomy and to detect atheromatous changes, occlusions, stenoses or tortuosity of the vessels of interest. Power settings were 120 kV, auto milliamperage, matrix of 512×512 pixels, collimation 64×1.25 mm, slice thickness 1.25 mm, and pitch 0.984:1. Iodinated contrast agent injection (150 mL, 350 mg I/mL, rate 4.5–5 mL/s) was performed with bolus triggering, with a region of interest (ROI) placed in the lower abdominal aorta just above the bifurcation. Scanning was initiated when the ROI reached a threshold of 300 Hounsfield units. In line with other authors (14), sagittal oblique maximum intensity projection (MIP) images were produced for delineation of the branching pattern of the internal iliac arteries (IIAs) and the origin of the prostatic arteries (PAs) and for correlation with angiography. Patients with occlusions or severe stenoses of the iliac arteries were not included in the study.

The baseline sonographic study (not earlier than 3 days before PAE) began with unenhanced, B-mode transabdominal ultrasonography (US) of the prostate, which was scanned in axial, coronal, and sagittal planes. Measurements of the maximum craniocaudal, anteroposterior and transverse diameters were made with electronic calipers on the screen of the US unit, and prostate volume (PV) was calculated with the ellipsoid formula. Post void residual volume (PVR) was also calculated with the same technique. Prostate enhancement was then studied by means of CEUS; a second generation echo-enhancer (1.2 mL of suspension of microbubbles of sulphur hexafluoride-SonoVue, Bracco), was admin-

istered as a bolus in an antecubital vein, followed by 5 mL flush of normal saline. The target organ was scanned in the same planes as the standard US for 120 seconds after the injection, with a contrast-specific, low mechanical index (MI= 0.09–0.13) algorithm. All sonographic studies were performed with a Logiq E9 XD clear US unit (General Electric, GE Healthcare) with CEUS capability and with a multifrequency (2–5 MHz), curved array transducer.

Technique of PAE

The patients were admitted to the urology department on the morning of the intervention. Thirty minutes prior to PAE, they received an intravenous dose of antibiotic (ceforadine, Radacef, 2 g), analgesic (parecoxib, Dynastat, 40 mg) and gastroprotective agent (ranitidine, Zantac, 50 mg). A Foley catheter was routinely inserted in the bladder and the retaining balloon was filled with a mixture of 30% iodinated contrast medium and 70% normal saline to facilitate anatomic orientation during angiography.

PAE was performed in the angio-suite (Axiom-Artis MP, Siemens Healthcare) under local anesthesia. Vascular access was obtained via the right or left common femoral artery with the Seldinger technique. The IIAs were catheterized with a 5 French (F) angiographic catheter. The uterine artery catheter (UAC, Merit Medical) along with a 0.032–0.035 inch curved tip, hydrophilic guidewire (Glidewire, Terumo Corp.) was used for catheterization of both the ipsilateral and contralateral IIA, with potential further advancement of the catheter tip distally into the splanchnic pelvic branches. When formation and maneuvering of the UAC was difficult, we utilized a catheter with a shorter distal limb (Cobra 1 or Contra 2, Boston Scientific) for the ipsilateral IIA. We used the same catheter with the glidewire to cross over the aortic bifurcation and to select the contralateral IIA. In cases of significant aortoiliac tortuosity, the glidewire was advanced distally into the contralateral IIA and the original catheter was exchanged with a hydrophilic one (Vertebral Glidecath, Terumo Corp.). Digital subtraction angiography (DSA) of the IIAs was performed with manual injection of 10–20 mL of contrast through the angiographic catheter, on standard (anteroposterior, AP) and ipsilateral anterior oblique (30°–40° with additional caudal-cranial angulation up to 10°) projections to identify the origin of the PAs. These were subsequently catheterized with a microcatheter (2.7 F Progreat, Terumo Corp.; 2.2 F Carnelian-Tokai Medical Products; 2.0 or 2.6 F Stridesmooth-Asahi Intecc Co.) and with the appropriate microguidewire. A double-angled 0.016-inch microguidewire (Meister-Asahi) was used to facilitate cannulation of acutely angled origins of PAs. After initial catheterization of the PAE, nitroglycerin (250 μg) was routinely administered through the microcatheter for vasodilation and additional angiograms were performed with manual injection of 2–4 mL of contrast through the microcatheter, on AP and oblique projections, to delineate the branching pattern of the PA. Embolization commenced at the distal extraprostatic part of the PA, and after advancement of the microcatheter beyond the potential origin of collateral branches to the bladder, rectum, or penis. When complete flow stasis was observed on the postembolization angiograms, distal advancement of the microcatheter into the intraprostatic branches was considered, as per "PErFecTED" technique ("Proximal Embolization First, Then Embolize Distal": first, embolization of the PA proximal to its branching to the central and peripheral zone; then, distal advancement of the microcatheter for intraprostatic embolization) (15). PAE was performed with microspheres (Embozene- Boston Scientific, or Embosphere-Merit Medical) with diameters of 100–700 μm.

A transabdominal CEUS study was occasionally performed in the angiographic suite, a few minutes after the completion of PAE and prior to the removal of the angiographic catheters and microcatheters (intraprocedural CEUS). The approach was similar to the one described for intraprocedural CEUS monitoring of liver tumor embolization (11). The technique was the same as for the baseline CEUS, with the exception of the shorter scanning time (scanning was terminated as soon as representative images of the prostate enhancement were acquired). In this study, intraprocedural CEUS was not a standard part of the protocol but rather an ancillary, optional technique which was utilized when there was adequate time, for a rapid evaluation of the local effect of PAE. The prostatic enhancement changes demonstrated by intraprocedural CEUS were only visually evaluated and no measurements of them were made. We considered its findings clinically relevant when: a) intraprocedural CEUS findings could help the operator to improve the local efficacy of PAE (e.g., inadequate devascularization of the treated hemiprostate is observed and the operator could perform additional embolization after a few minutes, or identify and embolize an additional PA at the same side), or b) intraprocedural CEUS findings could be used to expedite the PAE procedure (e.g., intraprocedural CEUS demonstrated adequate devascularization of the hemiprostate after standard PAE and application of the PErFecTED technique was not required).

Post PAE, all patients received intravenous fluids and antibiotics (ceforanide, 1 g ×2) and were observed overnight. For control of postembolization syndrome, nonopioid (panecoxib), or opioid (pethidine) analgesics were administered, depending on the severity of pain. Patients were asked to record perceived pain during PAE and during hospitalization with a visual analogue scale (VAS). Finally, they were discharged 18–24 hours post PAE, with prescription of oral antibiotics (cefuroxime, Zinadol, 500 mg ×2 for 5 days) and with instructions.

Postprocedural imaging

Follow-up with US and CEUS (similar to the preprocedural imaging) was performed in all patients 18–24 hours post PAE (1-day CEUS) and at approximately 1, 3, and 6 months post PAE. Postinterventional changes in PV and PVR were calculated from US measurements. Regarding CEUS, all pre- and postembolization scans were stored as digital video acquisitions in the hard-disk of the machine and were reviewed and compared to detect changes of prostate parenchymal enhancement, specifically well-defined, nonenhancing prostatic infarcts. The size of the infarcts on 1-day CEUS was measured in three dimensions, and the infarcted prostatic volume was calculated with the ellipsoid formula. The percentage of prostatic infarction (pPI) was calculated by dividing the volume of prostatic infarcts on 1-day CEUS by baseline PV (we utilized baseline PV instead of 1-day PV for the sake of simplicity, based on the assumption that prostate shrinkage 18–24 hours post PAE was negligible, therefore baseline PV was similar to 1-day PV). A unidimensional measurement (largest diameter) of the infarcts was performed on the other postprocedural CEUS studies.

Postprocedural CT was only performed when there were concerns for complications, which could have been diagnosed by

this modality. MRI was not included in the imaging protocol.

Postprocedural clinical evaluation and definition of success

At 1, 3, and 6 months post PAE, the urologists reevaluated the patients clinically and with uroflowmetry, and the IPSS and QoL questionnaires were updated. For the definition of technical and clinical success we adopted the criteria of a large previous PAE study (4). Technical success was defined as successful superselective catheterization and embolization of PA of at least one pelvic side. For clinical success, all three following requirements had to be met: (*i*) IPSS ≤ 15 points with a decrease of at least 25% from the baseline; (*ii*) QoL score ≤ 3 points or a decrease of at least 1 point from baseline; (*iii*) No additional medical or surgical treatment post PAE. For patients with IBC, clinical success should additionally have included successful and permanent catheter removal with spontaneous micturition and PVR <100 mL. In these patients, trials of catheter removal were performed every week for the first month post PAE and subsequently every 2 weeks. Complications were classified according to the Society of Interventional Radiology criteria (16).

Statistical analysis

Descriptive statistics were calculated for quantitative and qualitative data. The Kaplan-Meier method was used to calculate clinical success rates over time. The significance of the changes of the outcome parameters (baseline vs. 6-month values) was assessed with the Wilcoxon signed-rank test. The strength of correlation between the extent of prostatic infarcts and the improvement of outcome parameters was investigated with the Spearman correlation coefficient. Differences in outcomes between subgroups were evaluated with the Mann-Whitney U test and the Fisher's exact test. Statistical significance was defined as $P < 0.05$.

Results

Baseline demographic data of the study population and the reasons for selection of PAE are provided in Table 1. A technically successful PAE was achieved in 28 of 31 patients (90.3%). The 3 technical failures (6 pelvic sides) were attributed to a combination of tortuosity and multiple moderate stenoses of the iliac arteries and their branches (5 pelvic sides) and to inability for superselective catheterization of a PA which had a common origin with superior vesical artery (1 pelvic side). Bilateral PAE was performed in 21 patients and unilateral PAE in 7 (Figs. 1 and 2). Technical and other procedural details are provided in Table 2.

Table 1. Baseline demographic data and reasons for selection of PAE

Total number of patients (n)	31
Age (years), range (mean±SD)	58–88 (75.2±8.5)
Reason for selection of PAE	
Comorbidity precluding surgery (patients, n)	24/31
Diabetes mellitus	17/24
Cerebrovascular disease with stroke	5/24
Chronic obstructive pulmonary disease	8/24
Pulmonary hypertension	1/24
Congestive heart failure	5/24
Previous myocardial infarction	4/24
Atrial fibrillation on anticoagulants	2/24
Personal preference of the patient (patients, n)	7/31

PAE, prostatic artery embolization; SD, standard deviation.

Among patients with IBC (n=9), 4 had the catheter successfully removed 6–21 days (mean, 11 days) postintervention; 2 had successful removal of the Foley at 42 and 48 days post PAE, respectively. In 3 patients with IBC, spontaneous voiding could not be restored, despite multiple attempts and these patients were treated with transurethral resection (TUR) approximately 3 months post PAE. Histologic examination of the TUR specimens of the 3 surgically treated failures of PAE, confirmed the presence of microspheres in 2/3 patients (Fig. 3). Among patients with lower urinary tract symptoms (n=19, 4 patients with moderate and 15 with severe lower urinary tract symptoms), 14 patients experienced substantial improvement of their symptoms within the first days post PAE, 4 patients experienced a rather delayed clinical improvement (at 5–7 weeks post PAE) and one patient showed no improvement throughout the 6-month follow-up. Eventually this patient had to be managed with IBC.

Clinical follow-up data were available for 24 patients at 3 and 6 months post PAE (3 patients with technical failures and 4 early clinical failures were excluded). Follow-up data were also available at 9, 12, 15, and 18 months post PAE for 16, 13, 5, and 2 patients respectively (mean follow-up time, 9.7±4.3 months; median, 10.5 months; range, 6–18 months). Two additional clinical failures were observed: Twelve months post PAE, one patient from the IBC group had an increase of IPSS to 16 and a PVR of 140 mL; however he felt satisfied, had no sequelae of urinary retention and reinsertion of a Foley was not considered necessary by the urologist. Fifteen months post PAE, another patient was found with partial recurrence of his lower urinary tract symptoms (IPSS: 20). The cumulative clinical success rates at 3, 6, 12, and 15 months post PAE were 85.7%, 85.7%, 79.1%, and 59.3% respectively (Table 3) (Fig. 4).

Improvement of outcome parameters (baseline vs. 6-month values) was statistically significant with 12.4 points mean reduction of IPSS (50.4%, $P = 0.003$), 2.0 points mean reduction of QoL (45.4%, $P < 0.001$), 30.3 mL mean reduction of PV (30.2%, $P < 0.001$), 72.6 mL mean reduction of PVR (51.8%, $P = 0.005$) and 8.6 mL/s mean increase in Qmax (103%, $P = 0.002$) (Table 4).

According to VAS, the perceived pain during PAE and during hospitalization was generally minimal (mean, 0.70 and 0.52, respectively). There were two significant complications and both occurred after bilateral PAE with standard (not PErFecTED) technique and with 100 μm embolic: One patient presented with gross hematuria 2 days post PAE and CT showed ischemic changes, affecting a 47×42 mm area of the bladder wall. There was complete recovery

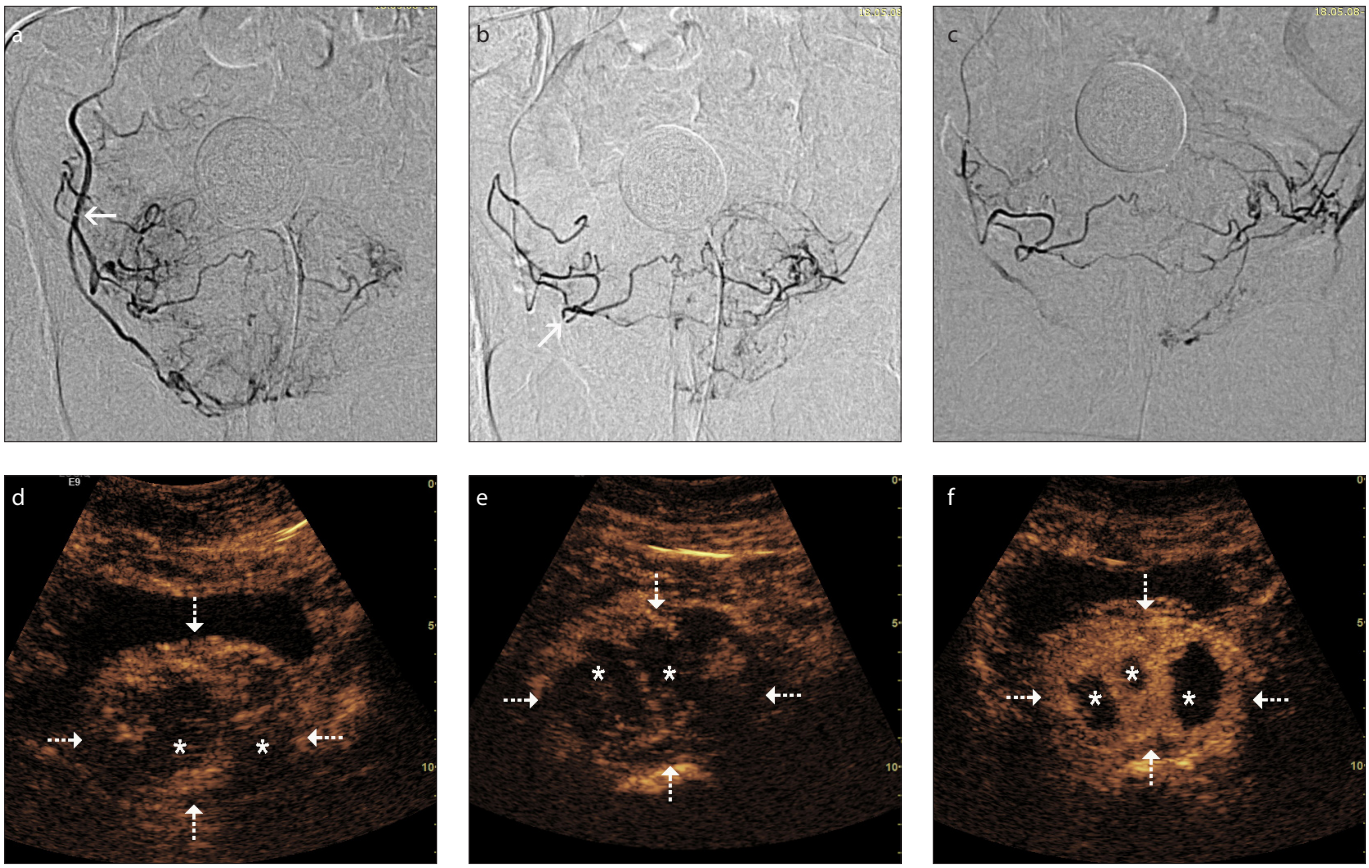

Figure 1. a–f. Representative case of unilateral prostatic artery embolization (PAE). Digital subtraction angiography (DSA) image anteroposterior (AP) projection prior to embolization **(a)**, shows the tip of the microcatheter in the right prostatic artery (PA) *(arrow)* and opacification of both prostatic lobes. Embolization (100–300 Embosphere) was first performed from the extraprostatic part of the right PA (not shown) and then the microcatheter was advanced distally. DSA image-AP projection **(b)**, shows the tip of the microcatheter *(arrow)* in an intraprostatic branch of the right lobe and extensive opacification of the left lobe through collaterals. Additional embolic was injected from this position. Postembolization DSA image-AP projection **(c)**, shows disappearance of prostatic parenchymal enhancement. Intraprocedural CEUS image **(d)**, shows bilateral nonenhancing prostatic infarcts, therefore L-PAE was not performed. One-day CEUS image **(e),** and 1-month CEUS image **(f)** also show prostatic infarcts. On all CEUS images, *asterisks* denote prostatic infarcts and *dotted arrows* indicate the borders of the prostate.

after bladder catheterization for 6 weeks and antibiotic treatment (13). The other patient complained of severe anal and perianal pain with onset 36 hours post PAE. CT performed 5 days later showed a partial thickness defect (diameter, 11 mm) of the right posterolateral rectal wall, indicative of ischemic rectal ulcer. The patient received antibiotics, laxatives and opioid analgesics and pain subsided 35 days post PAE. CT 5 months post PAE showed complete healing of the ulcer. Since both cases were managed on outpatient basis, they were recorded as class B complications; notably, they did not eventually affect the functional improvement which was significant (both patients were recorded as clinical successes 3 months post PAE). There were 2 additional class B complications (acute urinary retention requiring bladder catheterization for a few days post PAE, n=2), and 4 class A complications: transient minor hematuria (n=1), transient minor rectal bleeding (n=1), urethral burning and pain (n=2).

Intraprocedural CEUS was performed in 16 patients. Poor image quality rendered 2 of these examinations (12.5%) nondiagnostic, while it provided clinically relevant information in 6 of the 14 other patients (42.8%): In 2 of 6 patients, intraprocedural CEUS showed adequate infarction of both prostatic lobes after unilateral embolization, thus obviating the need for investigation and cannulation of the contralateral PA. In 4 of 6 patients, intraprocedural CEUS demonstrated adequate infarction of the treated side after embolization of the proximal PA, and therefore additional application of the technically demanding "PErFecTED" technique was not required. In the remaining 8 patients intraprocedural CEUS showed ischemic changes, but the operators could not exploit this finding to improve the outcome or to expedite the procedure.

Prostatic infarcts were also the primary finding of 1-day CEUS. They were detectable in 26 of the 28 treated patients (92.8%). In these 26 patients, the volume of prostatic infarcts ranged from 1.5 to 59 mL (median, 20.5 mL; mean, 23.4±16.6 mL). The percentage of prostatic infarction (pPI: volume of prostatic infarcts on 1-day CEUS divided by baseline PV) was 1%–71% (median, 17.5%; mean, 25.1%±18.1%). Notably, there was a very strong correlation between pPI and the degree of prostate shrinkage (PV reduction compared to baseline) at 6 months. On the contrary, only weak and not statistically significant correlations were found between pPI and the improvement of other outcome parameters (Table 5). However, in the subgroup of patients with IBC, successful removal of the catheter was achieved only in 6 of 9 patients with pPI >10% (11.4%–43.6%; median, 23.3%; mean, 25.8%±14.3%). CEUS follow-up of prostatic infarcts revealed a gradual reduc-

Table 2. Summary of technical and safety aspects of the PAE procedures performed on the patients (n=31) in this study

Procedure time (min), mean±SD	105.2±30.2
Fluoroscopy time (min), mean±SD	57.6±19.3
Technical success (patients, n)	28/31
Unilateral/bilateral PAE (patients, n)	7/21
"PErFecTED" / Original technique (patients, n)[a]	10/18
"PErFecTED" / Original technique (pelvic sides)	12/37
Utilization of microspheres per diameter (pelvic sides)	
100 μm[b]	8
100–300 μm	16
300–500 μm	17
500–700 μm[c]	3
Combination	5
Complications (patients, n)	
Class A	4
Class B	4

PAE, prostatic artery embolization; SD, standard deviation.
[a]A patient was recorded as treated with PErFecTED technique, even though this technique had been performed in only one pelvic side.
[b]The types of microspheres were Embozene 100 for 100 μm, Embosphere 100–300 or Embozene 250 for 100–300 μm, Embosphere 300-500, Embozene 400, or Embozene 500 for 300–500 μm, Embosphere 500–700 or Embozene 700 for the diameter of 500–700 μm.
[c]Microspheres larger than 500 μm were utilized in case of large intraprostatic anastomoses of the prostatic arteries with the penile arteries, when it was not possible to reach and protect these anastomoses by coiling. An example is shown in Fig. 2.

Table 3. Cumulative data of clinical effectiveness of PAE during follow-up

	3 months	6 months	12 months	15 months
Patients at risk (n)	24	24	13	5
Cumulative clinical failures (n)	4	4	5	6
Cumulative clinical success rate (%)	85.7	85.7	79.1	59.3

PAE, prostatic artery embolization.

tion in size and number and eventual disappearance of many of them: From the baseline mean value of 34±14 mm, the largest diameter of the infarcts was reduced to 28.2±13.9 mm at 1-month CEUS (infarcts detected in 26/28 patients), 14.1±6.9 mm at 3-month CEUS (in 21/28 patients) and 14.3±2.6 mm at 6-month CEUS (in 17/28 patients). Differences in pPI and clinical success rates between subgroups are shown in Table 6.

Discussion

In this work we described our experience on CEUS-imaging follow-up of PAE for the treatment of symptomatic BPH; we also provided relevant data on the technical application, clinical effectiveness and safety of PAE. From a technical perspective, some of our results (technical success, procedural and fluoroscopy times) are comparable to those of earlier or smaller studies (17, 18), but inferior to those reported from high-volume centers with experienced operators (technical success >95%, mean procedure time <80 min, mean fluoroscopy time <40 min) (4, 8). PAE is often a time consuming and technically demanding intervention, because of the complex and variable arterial anatomy, the small size of the target arteries and coexisting atherosclerotic changes. Two additional factors could have affected our technical outcomes: First, our study population was quite old (older than that of the majority of the other studies) and more likely to have extensive atheromatous changes of the pelvic arteries. Second, we had not applied strict criteria for exclusion of patients on the basis of planning CTA, therefore many of the treated patients had tortuous vessels and moderate stenoses.

Despite these difficulties, our short-term clinical success rate of 79.1%–85.7% is considered satisfactory and is derived from a statistically significant improvement of all the outcome parameters. This supports the role of PAE as an effective alternative to the standard operative urological treatments, particularly for patients unfit for surgery. Short-to mid-term success rates are 72.1%–98% (19, 20, 21) and among several studies, improvement in outcome parameters varies from 31%–85% for IPSS, 29%–81% for QoL, 17%–132% for Qmax, 5%–45% for PV and 35%–76% for PVR (5, 22).

In 6 of our 28 treated patients (21.4%) clinical success appeared after the first month post PAE. We believe that in the aforementioned patients, clinical improvement was primarily associated with prostate debulking (i.e., with the static component of BPH (6) and not with functional or hormonal mechanisms). Since prostate shrinkage post PAE is not rapid, but evolves over several weeks (10), it is not surprising that some patients experience a relatively delayed clinical improvement. This observation has also been made by others (23) and should not discourage the patient or the physician.

Our interventions were complicated by 2 cases of nontarget embolization. We hypothesize that bladder ischemia was caused by reflux of microspheres into the superior vesical arteries. Rectal ischemia was most likely caused by nonrecognition and inadvertent embolization of a prostatic-middle rectal anastomosis. Utilization of cone-beam CT could have prevented this complication. Moreover, microspheres of relatively small diameters are considered to penetrate deep into the small arterial branches and to cause more extensive prostatic ischemia than larger ones (20). However, smaller embolics might also be associated with greater risk of tissue necrosis in case of nontarget embolization.

A distinctive feature of this study is the utilization of CEUS instead of CEMRI for the

Table 4. Values of outcome parameters pre- and post-PAE and significance of their changes

	Baseline	1-month post PAE	3-month post PAE	6-month post PAE	*P* vs. baseline
PV (mL) (n=28)	94 (56–150)	84.5 (57–154)	57 (50–130)	58 (44–120)	1-month post PAE: 0.264
					3-month post PAE: <0.001
					6-month post PAE: <0.001
PVR (mL) (n=28)	140 (35–240)	67.5 (30–180)	44.5 (30–97)	40 (5–98)	1-month post PAE: 0.058
					3-month post PAE: 0.003
					6-month post PAE: 0.005
Qmax (mL/s) (n=28)	8.1 (4.4–9.9)	15 (7.3–18.2)	15.6 (9.9–21.8)	17.1 (10.1–22.9)	1-month post PAE: 0.003
					3-month post PAE: 0.003
					6-month post PAE: 0.002
IPSS (n=28)	25 (19–32)	15 (6–32)	13.5 (6–15)	12 (4–15)	1-month post PAE: 0.007
					3-month post PAE: 0.003
					6-month post PAE: 0.003
QoL (n=28)	5 (3–5)	3.5 (2–6)	2.5 (1–3)	2.5 (1–3)	1-month post PAE: 0.005
					3-month post PAE: <0.001
					6-month post PAE: <0.001

Data are presented as median (min–max). Sample size (n) represents the number of patients who underwent technically successful PAE. Further details are provided in the text.
PV, prostatic volume; PVR, post void residual volume; Qmax, maximum urinary flow; IPSS, International prostate symptom score; QoL, quality of life.

Table 5. Correlation between the percentage of prostatic infarction and the improvement of outcome measures in patients with technically successful PAE (n=28)

	PV reduction	PVR reduction	IPSS reduction	QoL reduction	Qmax increase
r	0.813	0.173	0.014	0.357	0.192
P	<0.001	0.611	0.965	0.093	0.619

PAE, prostatic artery embolization; PV, prostatic volume; PVR, post void residual volume; IPSS, International prostate symptom score; QoL, quality of life; Qmax, maximum urinary flow; r, Spearman correlation coefficient.

Table 6. Percentage of prostatic infarction (pPI) and clinical success in different subgroups of patients[a]

	pPI mean/median (min–max)%	*P*	Clinical success[b] (patients, n)	*P*
Unilateral PAE	11.6/12.9 (0–31)	0.038	4/7	0.037
Bilateral PAE	27.8/21.4 (1–71)		20/21	
PErFecTED PAE	38.3/31 (17.5–71)	0.010[a]	10/10	0.265
Original PAE	17.3/14.3 (0–43.6)		14/18	
PV ≤90 mL	24.2/16.6 (0–71)	0.841	8/9	1.00
PV >90 mL	20.2/16.1 (1–54)		16/19	

PAE, prostatic artery embolization; PV, prostatic volume.
[a]The results should be viewed with caution because of the small number of patients and of confounding factors. For example, the "PErFecTED" technique was usually performed with smaller microspheres than the original technique, and the smaller size of microspheres may have contributed to the greater extent of ischemia.
[b]At 6 months post PAE.

serial evaluation of the ischemic effect of PAE. There are some advantages of CEUS over CEMRI in this context. CEUS can be performed with affordable equipment; the echo enhancer is extremely safe and CEUS with modern machines is cost-effective, as only 1.2 mL (1/4 of each vial) of echo-enhancer is required for each study. Technically, CEUS is faster and more flexible than MRI and can be performed in the angio-suite to guide the procedure. CEUS equipment is available in our department since 2004 and we utilize extensively this modality for monitoring of interventional procedures. On the other hand, limitations in the availability of MRI as well as socioeconomic and health insurance issues would have caused us great difficulties in performing repeated MRI studies in all our patients.

In the absence of relevant CEUS studies, we attempted to correlate our results with existing evidence from post PAE CEMRI studies (7–10). Compared with the latter (8), we recorded a higher mean volume of prostate infarction post PAE (23.4 mL vs. 11.6 mL) and higher mean pPI (25.1% vs. 11%), but our results were based on 1-day CEUS (vs. CEMRI within 1 month of PAE) and there were several other major methodologic differences (8).

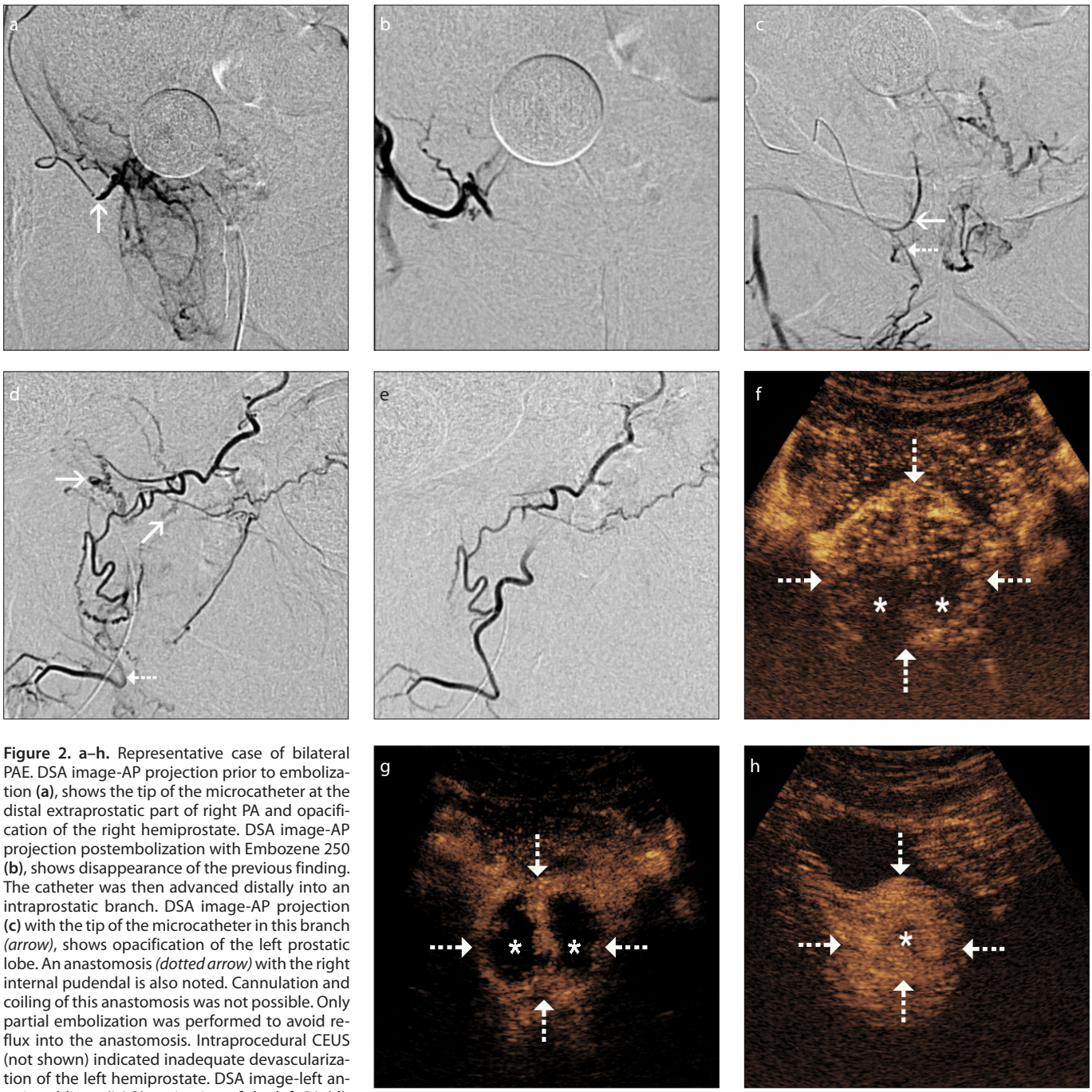

Figure 2. a–h. Representative case of bilateral PAE. DSA image-AP projection prior to embolization **(a)**, shows the tip of the microcatheter at the distal extraprostatic part of right PA and opacification of the right hemiprostate. DSA image-AP projection postembolization with Embozene 250 **(b)**, shows disappearance of the previous finding. The catheter was then advanced distally into an intraprostatic branch. DSA image-AP projection **(c)** with the tip of the microcatheter in this branch *(arrow)*, shows opacification of the left prostatic lobe. An anastomosis *(dotted arrow)* with the right internal pudendal is also noted. Cannulation and coiling of this anastomosis was not possible. Only partial embolization was performed to avoid reflux into the anastomosis. Intraprocedural CEUS (not shown) indicated inadequate devascularization of the left hemiprostate. DSA image-left anterior oblique (LAO) projection of the left PA **(d)**, shows several tortuous intraprostatic branches *(arrows)* and intraprostatic anastomosis with the penile artery *(dotted arrow)*. Further advancement of the microcatheter was not possible and PAE was performed with larger agents (Embozene 700). DSA image-LAO projection post PAE **(e)**, shows disappearance of the prostatic branches and preserved flow to the penile artery. Intraprocedural CEUS image **(f)** a few minutes post L-PAE, shows bilateral nonenhancing prostatic infarcts. One-month CEUS image **(g)**, shows the infarcts more clearly. Six-month CEUS image **(h)**, shows almost complete disappearance of the infarcts. On all CEUS images, *asterisks* denote prostatic infarcts and *dotted arrows* indicate the borders of the prostate. Prostate shrinkage is also noted on **(h)**. No deterioration of the erectile function was reported.

Regarding the predictive value of our findings, it is noteworthy that they correlate well with those of some CEMRI studies: Both CEUS and CEMRI indicate a good correlation between infarction post PAE and prostate shrinkage (8–10). It is almost certain that ischemic infarction is one of the modes of the therapeutic action of PAE. The infarcted nodules of BPH eventually shrink and their mass effect on the prostatic urethra is relieved (6, 10). But it is also likely that additional mechanisms play a role: Less severe ischemia (which may not be demonstrated as infarcts on CEUS) may still induce debulking and symptomatic improvement by causing apoptosis of the glandular prostatic tissue. Reduced blood supply to the prostate additionally blockades the transport of testosterone and dehydrotestosterone to the organ, resulting again in apoptosis. Finally, ischemia may cause functional improve-

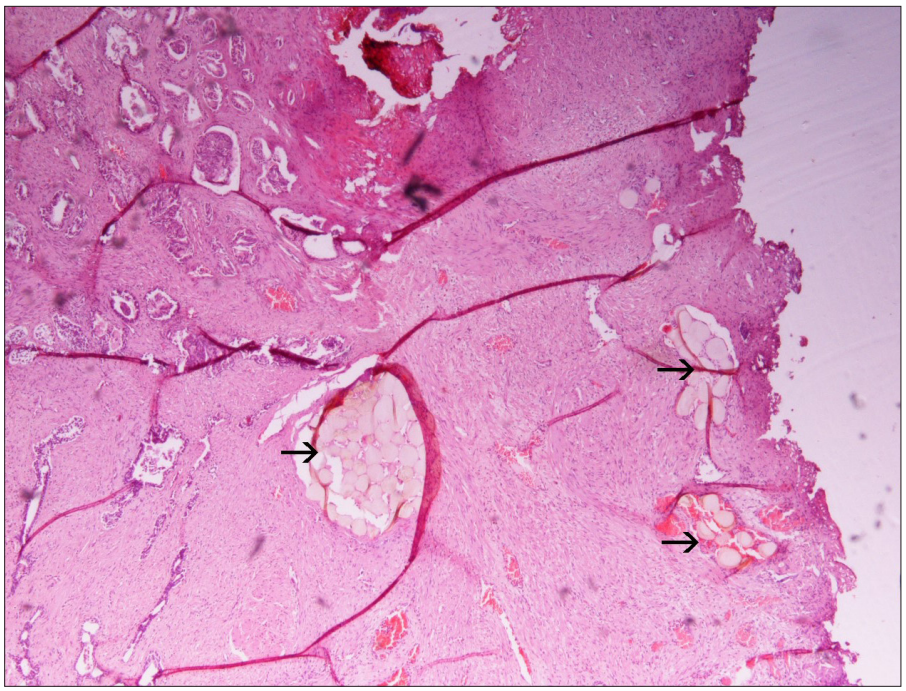

Figure 3. Image from histologic examination (hematoxylin-eosin stain, original magnification ×4) of a transurethral resection (TUR) specimen following failed PAE shows aggregates of eosinophilic, 100 µm microspheres *(arrows)* filling the vascular spaces with diameters of approximately 400–650 µm, but no significant necrosis.

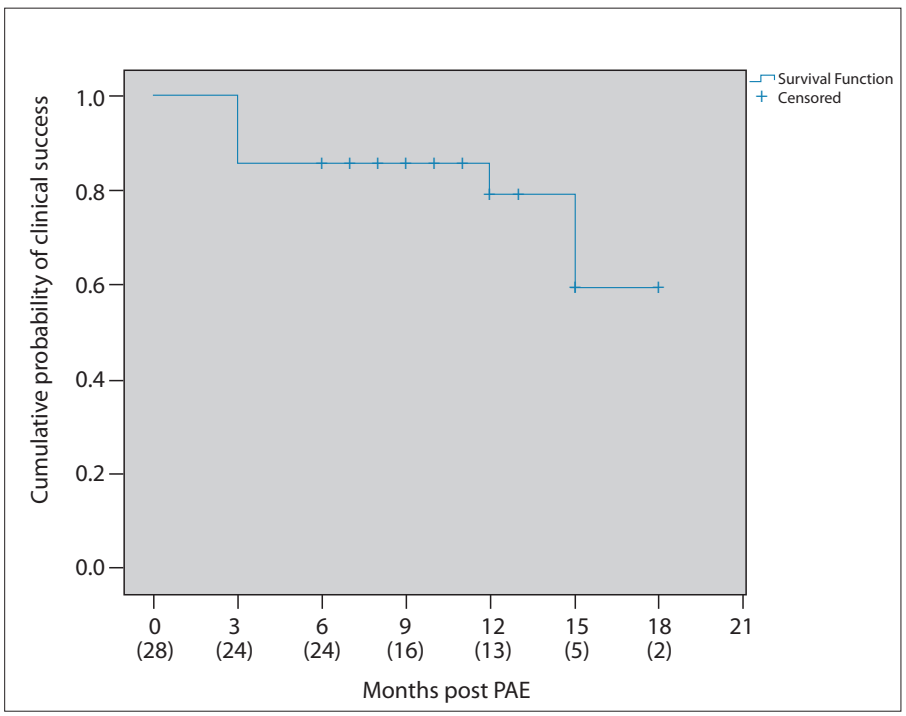

Figure 4. Graph shows the Kaplan-Meier estimates of the cumulative probability of clinical success after PAE. The numbers of patients at risk are shown in parentheses below each time point.

ment by reducing the tone of the smooth muscle of the prostate through the damage of α1-adrenergic receptors of the embolized area (6). Our results, as well as those of CEMRI studies provide evidence regarding the correlation between prostatic ischemia (infarction) and clinical effectiveness. In our subgroup of IBC patients, pPI could predict successful catheter removal; in our entire cohort we found no significant correlation between pPI and the improvement of clinical outcomes, but this was probably due to the small sample size. In a study of a larger population (8), the proportion of prostatic ischemia detected by MRI in the first month post PAE correlated strongly with the decrease of IPSS (P = 0.009). In another MRI study of patients with IBC, ischemic infarcts induced by PAE were considered as the best predictor of clinical success (7). Contrasting evidence does exist: In a recent study (23), PAE-induced changes of surrogate MRI parameters of prostate vascularization could not predict clinical outcomes; however, the volume of prostate ischemia was not calculated.

We studied unilateral PAE with CEUS and we highlighted cases of bilateral infarction after unilateral embolization. Overall, however, we documented the inferiority of unilateral compared to bilateral PAE, in terms of the extent of ischemia (mean pPI, 11.6% vs. 27.8%) and of clinical success. On the other hand, both CEUS outcomes (pPI) and clinical outcomes were not significantly different when we compared PAE of smaller prostates (<90 mL) with that of larger prostates. These observations are also in line with previous studies (8, 24).

Evaluation of the intraprocedural role of CEUS was not the main objective of our study, nevertheless our initial experience showed that CEUS could be performed in the angio-suite, to capture the ischemic effect of PAE, only a few minutes after the injection of the embolic. This provided a valuable immediate feedback, which increased the confidence of the operator and occasionally guided further decisions (regarding, for example, the necessity to proceed to "PErFecTED" technique, or to contralateral PAE).

Several limitations are associated with the present work: Our study population was relatively small and inhomogeneous. We used embolics of different types and diameters; this inconsistency is a serious limitation for a prospective study and was associated with the availability of each embolic at the time of intervention and with the preferences of the operator. No long-term follow-up was available. Our method for the calculation of the infarcted prostatic volume was not accurate (particularly for irregularly shaped infarcts) and we did not utilize transrectal US (TRUS)/TRCEUS, which could have provided a more detailed depiction of the infarcts (12). However, TRUS is less well tolerated by the patients than

transabdominal US. Finally, our US/CEUS findings were not compared with those of a "gold standard" technique (i.e., MRI).

In conclusion, our results highlight the potential role of CEUS, as an effective modality for intra- and postprocedural imaging evaluation of PAE. In this context, prostatic infarcts represent a valuable, easily identifiable feature; however, in-depth understanding of the therapeutic mechanisms of PAE probably requires a more sophisticated, multiparametric and multimodality imaging approach.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Mitchell ME, Waltman AC, Athanasoulis CA, Kerr WS Jr, Dretler SP. Control of massive prostatic bleeding with angiographic techniques. J Urol 1976; 115:692–695. [CrossRef]
2. Pyo JS, Cho WJ. Systematic review and meta-analysis of prostatic artery embolisation for lower urinary tract symptoms related to benign prostatic hyperplasia. Clin Radiol 2017; 72:16–22. [CrossRef]
3. Petrillo M, Pesapane F, Fumarola EM, et al. State of the art of prostatic arterial embolization for benign prostatic hyperplasia. Gland Surg 2018; 7:188–199. [CrossRef]
4. Pisco JM, Bilhim T, Pinheiro LC, et al. Medium- and long-term outcome of prostate artery embolization for patients with benign prostatic hyperplasia: results in 630 patients. J Vasc Interv Radiol 2016; 27:1115–1122. [CrossRef]
5. Teichgräber U, Aschenbach R, Diamantis I, von Rundstedt FC, Grimm MO, Franiel T. Prostate artery embolization: indication, technique and clinical results. Rofo 2018; 190:847–855. [CrossRef]
6. Sun F, Crisóstomo V, Báez-Díaz C, Sánchez FM. Prostatic artery embolization (PAE) for symptomatic benign prostatic hyperplasia (BPH): Part 2, insights into the technical rationale. Cardiovasc Intervent Radiol 2016; 39:161–169. [CrossRef]
7. Kisilevzky N, Faintuch S. MRI assessment of prostatic ischaemia: best predictor of clinical success after prostatic artery embolisation for benign prostatic hyperplasia. Clin Radiol 2016; 71:876–882. [CrossRef]
8. Bilhim T, Pisco J, Pereira JA, et al. Predictors of clinical outcome after prostate artery embolization with spherical and nonspherical polyvinyl alcohol particles in patients with benign prostatic hyperplasia. Radiology 2016; 281:289–300. [CrossRef]
9. Little MW, Boardman P, Macdonald AC, et al. Adenomatous-dominant benign prostatic hyperplasia (AdBPH) as a predictor for clinical success following prostate artery embolization: an age-matched case-control study. Cardiovasc Intervent Radiol 2017; 40:682–689. [CrossRef]
10. Lin YT, Amouyal G, Correas JM, et al. Can prostatic arterial embolisation (PAE) reduce the volume of the peripheral zone? MRI evaluation of zonal anatomy and infarction after PAE. Eur Radiol 2016; 26:3466–3473. [CrossRef]
11. Moschouris H, Malagari K, Kornezos I, Papadaki MG, Gkoutzios P, Matsaidonis D. Unenhanced and contrast-enhanced ultrasonography during hepatic transarterial embolization and chemoembolization with drug-eluting beads. Cardiovasc Intervent Radiol 2010; 33:1215–1222. [CrossRef]
12. Moschouris H, Stamatiou K, Kalokairinou Motogna M, et al. Early post-interventional sonographic evaluation of prostatic artery embolization. A promising role for contrast-enhanced ultrasonography (CEUS). Med Ultrason 2018; 20:134–140. [CrossRef]
13. Moschouris H, Stamatiou K, Kornezos I, Kartsouni V, Malagari K. Favorable outcome of conservative management of extensive bladder ischemia complicating prostatic artery embolization. Cardiovasc Intervent Radiol 2018; 41:191–196. [CrossRef]
14. Bilhim T, Pisco JM, Rio Tinto H, et al. Prostatic arterial supply: anatomic and imaging findings relevant for selective arterial embolization. J Vasc Interv Radiol 2012; 23:1403–1415. [CrossRef]
15. Carnevale FC, Moreira AM, Antunes AA. The "PErFecTED technique": proximal embolization first, then embolize distal for benign prostatic hyperplasia. Cardiovasc Intervent Radiol 2014; 37:1602–1605. [CrossRef]
16. Omary RA, Bettmann MA, Cardella JF, et al; Society of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for the reporting and archiving of interventional radiology procedures. J Vasc Interv Radiol 2003; 14:293–295. [CrossRef]
17. Carnevale FC, da Motta-Leal-Filho JM, Antunes AA, et al. Quality of life and clinical symptom improvement support prostatic artery embolization for patients with acute urinary retention caused by benign prostatic hyperplasia. J Vasc Interv Radiol 2013; 24:535–542. [CrossRef]
18. Li Q, Duan F, Wang MQ, et al. Prostatic arterial embolization with small sized particles for the treatment of lower urinary tract symptoms due to large benign prostatic hyperplasia: preliminary results. Chin Med J (Engl) 2015; 128:2072–2077. [CrossRef]
19. Christidis D, Clarebrough E, Ly V, et al. Prostatic artery embolization for benign prostatic obstruction: assessment of safety and efficacy. World J Urol 2018; 36:575–584. [CrossRef]
20. Bilhim T, Pisco J, Campos Pinheiro L, et al. Does polyvinyl alcohol particle size change the outcome of prostatic arterial embolization for benign prostatic hyperplasia? Results from a single-center randomized prospective study. J Vasc Interv Radiol 2013; 24:1595–1602. [CrossRef]
21. Pisco J, Bilhim T, Pinheiro LC, et al. Prostate embolization as an alternative to open surgery in patients with large prostate and moderate to severe lower urinary tract symptoms. J Vasc Interv Radiol 2016; 27:700–708. [CrossRef]
22. Shim SR, Kanhai KJ, Ko YM, Kim JH. Efficacy and safety of prostatic arterial embolization: systematic review with meta-analysis and meta-regression. J Urol 2017; 197:465–479. [CrossRef]
23. Franiel T, Aschenbach R, Trupp S, et al. Prostatic artery embolization with 250-µm spherical polyzene-coated hydrogel microspheres for lower urinary tract symptoms with follow-up MR imaging. J Vasc Interv Radiol 2018; 29:1127–1137. [CrossRef]
24. Bilhim T, Pisco J, Rio Tinto H, et al. Unilateral versus bilateral prostatic arterial embolization for lower urinary tract symptoms in patients with prostate enlargement. Cardiovasc Intervent Radiol 2013; 36:403–411. [CrossRef]