Early post-interventional sonographic evaluation of prostatic artery embolization. A promising role for contrast-enhanced ultrasonography (CEUS)

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Abstract
Aims: To assess the feasibility, findings and potential value of early post-interventional, contrast-enhanced ultrasonographic (CEUS) study of prostate artery embolization (PAE). Material and methods: Fourteen patients treated with PAE for symptomatic benign prostatic hyperplasia were prospectively included in the study. Sonographic evaluation of the prostate included: 1) baseline transabdominal and transrectal CEUS (ta-CEUS and tr-CEUS, respectively) 1-3 days prior to PAE; 2) early post PAE CEUS, with ta-CEUS immediately post PAE and tr-CEUS 3 days post PAE; and 3) follow-up with ta-CEUS and tr-CEUS 3 months post PAE. A brief unenhanced US study preceded each CEUS. Post-therapeutic changes in size, echogenicity and enhancement of the prostate were recorded and were correlated with clinical outcomes. Results: PAE resulted in clinical success in 11/14 patients (78.5%). All sonographic studies were technically adequate, with the exception of ta-CEUS immediately post PAE in 2/14 (14.2%) patients. CEUS studies immediately post PAE and 3 days post PAE showed non-enhancing, well-defined infarctions of the prostate in 10/14 patients (71.4%). There was a strong correlation between ta-CEUS immediately post PAE and tr-CEUS 3 days post PAE regarding the measurements of prostatic infarctions (r=0.98, p< 0.01). The presence of infarctions on early post PAE CEUS was associated with clinical success (p=0.01) and their extent correlated with the degree of prostate shrinkage on 3-month follow-up (r=0.84, p<0.05). The 3 cases of failed PAE showed no infarctions and no prostate shrinkage. Conclusions: Early post-interventional CEUS of PAE is feasible and may have clinical and prognostic value.

Keywords: prostatic artery embolization; benign prostatic hyperplasia; contrast-enhanced ultrasonography; prostatic infarctions

Introduction
Prostatic artery embolization (PAE) is a relatively new, minimally invasive endovascular treatment of symptomatic benign prostatic hyperplasia (BPH). In this context, PAE has demonstrated an attractive profile of safety and efficacy and is gaining acceptance as a valid alternative to surgical treatments [1]. Along with clinical and urodynamic parameters, imaging plays an important role in the evaluation of the therapeutic benefit of PAE [2]. For this purpose, magnetic resonance imaging (MRI) is currently considered the most powerful imaging tool, since it can provide both morphologic and hemodynamic information that reflect the effect of embolization on the hyperplastic prostatic tissue [3]. B-mode ultrasonography (US) has also been used for the evaluation of PAE [1,2]. However, US can assess only morphologic features of the prostate (primarily its volume and shape) and the respective changes usually appear several weeks post
PAE. Previous experience with contrast-enhanced ultrasoundography (CEUS) in liver embolization indicates that this modality can detect perfusional changes that occur very early within the treated tumors and that CEUS findings correlate favorably with those of follow-up with reference imaging modalities [4]. The application of CEUS for the assessment of the efficacy of PAE is at present very limited [2,5,6]; moreover, the majority of the respective examinations were performed weeks or months post PAE and had not been correlated with the clinical outcomes.

In this work, we utilized sonography (US and CEUS) as the primary imaging modality for the assessment of patients treated with PAE for symptomatic BPH. We herein report on our experience with emphasis on early CEUS findings and on their potential clinical relevance.

Materials and methods

Patients

This was a prospective study of male patients who were treated with PAE for symptomatic BPH in our institution from October 2016 until July 2017. Inclusion criteria were: age >50 years; moderate-to-severe lower urinary tract symptoms (International Prostate Symptom Score, IPSS >18) refractory to medical treatment (5α-reductase inhibitors or selective α1 blockers) for at least 6 months, or urinary retention managed with indwelling bladder catheter, with at least 3 failed attempts of catheter removal prior to PAE; prostate with a volume of at least 35 ml (calculated by transrectal US).

Patients with previous surgical or interventional prostate treatments, urinary tract infection, prostate or bladder cancer, neurogenic bladder, large (>3 cm) bladder diverticula or bladder stones were excluded from the study. Contraindications to angiographic procedures and non-compliance with the imaging follow-up schedule were also exclusion criteria. The procedure and the required diagnostic work-up were discussed in detail with the patients, and written informed consent was obtained from them. The institutional review board approved the study.

Technique of PAE

Vascular access was obtained via the right or left common femoral artery with the Seldinger technique. The internal iliac arteries were catheterized with a 5 French (Fr.) angiographic catheter (Cobra 1 or Contra 2, Boston Scientific, MA, USA, or Uterine artery catheter, Merit Medical, South Jordan, UT, USA) and with a 0.035” hydrophilic guidewire (Glidewire, Terumo Corporation, Japan). Internal iliac angiograms were performed on standard (anteroposterior) and ipsilateral anterior oblique projections to identify the origin of the prostatic arteries (PAs). These were subsequently catheterized with a microcatheter (2.7 Fr. Progreat, Terumo, or 2.0Fr. Stride, Asahi Intec co, Japan). In the absence of significant anastomoses between PA and other pelvic arteries, embolization of the PA was performed with microspheres (Embozene, Boston Scientific, with diameters of 100 μm, 250 μm or 500 μm or Embosphere, Merit Medical, with diameters of 100-300 μm, 300-500 μm or 500-700 μm) until complete flow stasis was observed on post-embolization angiograms. The following technical features were recorded, in order to be correlated with the imaging findings: a) unilateral versus bilateral PAE. b) proximal PAE (with the microcatheter tip near the origin of the PA), versus distal PAE (with the microcatheter tip at the distal part of the PA, or in intraprostatic branches); c) diameter of the microspheres which were utilized in each case. Clinical success of PAE in patients with indwelling bladder catheter was defined as removal of the catheter and spontaneous urination within 30 days post PAE. For the rest of the patients, PAE was considered successful, if it resulted in reduction of IPSS of at least 25% from the baseline value, with an absolute value lower than 15, within 1 month post intervention.

Sonographic evaluation

This consisted of: 1) a baseline study (performed 1-3 days prior to PAE) which included unenhanced, B-mode ultrasonography (US) of the prostate with transabdominal and transrectal approach (ta-US and tr-US, respectively) and CEUS with similar approaches (ta-CEUS and tr-CEUS, respectively); 2) an early post PAE study with 2 parts: A ta-CEUS study performed in the angiographic suite, a few minutes after the completion of PAE, and a tr-CEUS performed approximately 3 (2-4) days post PAE, on outpatient basis; 3) a follow-up study 3 months post PAE with the same protocol as the baseline study.

All US studies were performed with high-end ultrasonographic equipment (General Electric Logiq E9 XD-clear, GE Healthcare, Milwaukee, WI, USA) with CEUS capability. A multifrequency (2-5 MHz), curved array transducer was used for transabdominal imaging and a 4-9 MHz, wideband, endocavity microconvex probe for transrectal imaging.

The objective of the unenhanced US studies was to measure the prostatic volume (PV). The prostate was scanned in axial, coronal and sagittal plane. The maximum craniocaudal (length) and anteroposterior (height) diameters were measured in the sagittal plane and the maximum transverse diameter (width) was measured in the axial plane. PV was calculated with the ellipsoid formula (length x height x width x 0.52).

The objective of CEUS was to study the enhancement of the entire prostate gland and to compare pre- and post-
embolization scans, in order to detect and measure any clearly visible and well-defined changes of the prostate parenchymal enhancement that could have been attributed to PAE. For CEUS, a second generation ultrasound contrast agent (suspension of microbubbles of sulphur hexafluoride, SonoVue, Bracco, Milan Italy), was injected as a 1.2 ml bolus in a forearm vein, followed by a 5 ml flush of normal saline 0.9%. A dedicated, contrast specific, continuous scanning, low mechanical index (MI=0.09-0.13) algorithm and the default settings for “General Frequency” CEUS were utilized; the prostate was scanned in three planes for at least 120 seconds after the injection. Focus was set with one point to the deepest edge of the gland. A “split-screen” display was constantly utilized, which showed a low MI, low resolution, reference B-mode image on the left and the corresponding CEUS image on the right half of the screen. All sonographic examinations were performed by the same operator, who had 13 years of experience in urogenital CEUS imaging. Transabdominal studies always preceded the transrectal ones. At the time of post-PAE studies the operator was aware of the angiographic findings.

**Statistical Analysis**

Descriptive statistics were calculated for quantitative and qualitative data. The normality of distribution of numerical variables was assessed with the Shapiro-Wilk test. The significance of changes in PV (baseline versus 3 months post PAE) were evaluated with the Wilcoxon Signed-Rank test. The strength of correlation between measurements of transrectal and transabdominal scanning was investigated with the Pearson correlation coefficient (r). Post-therapeutic changes in the enhancement of the prostate were correlated with the clinical outcome with the Fisher’s exact test. Statistical significance was defined as a p value of <0.05. Statistical analysis was performed with SPSS 19.0 (SPSS Inc., Chicago, IL).

**Results**

Fourteen patients (age: 59-83, mean: 73 years) were prospectively enrolled in the study. Bilateral PAE was achieved in 8 patients and unilateral PAE in 6. The intervention resulted in clinical success in 11/14 patients (78.5%): There were 6 patients with indwelling bladder catheter, in whom the catheter was successfully removed in 4 to 20 (mean: 11) days post intervention; additionally, there were 5 patients who experienced a significant improvement of their BPH-related symptoms, with a 71% mean reduction of their IPSS (from a mean of 27.5 at baseline to a mean of 8 within thirty days from PAE). No recurrences had been observed in patients with clinical success during the 3 months of follow-up. PAE failed in 3 patients: in one of them removal of the indwelling catheter proved unsuccessful in all 3 trials that were performed post PAE. The other 2 patients experienced no improvement of their symptoms.

All sonographic studies were technically adequate, with the exception of 2 ta-CEUS examinations, which suffered from poor image quality and from incomplete depiction of the prostatic enhancement. Superimposed bowel gas and patient intolerance to pressure with the transducer were the most likely causes. US and CEUS studies were performed with a bladder volume ranging from 95 to 260ml. Measurements of the prostate volume are provided in table I. A strong correlation was found between tr-US and ta-US (r=0.99, p<0.01 for baseline measurements and r=0.98, p<0.01 for 3 months follow-up. The changes in PV at 3 months follow-up compared to baseline PV were significant (p<0.05 for both approaches).

On baseline CEUS studies, all the prostates showed relatively intense and homogeneous enhancement. Tiny non-enhancing areas, with a volume less than 1% of the total prostatic volume were detected in 3 prostates (both on ta-CEUS and on tr-CEUS) and were attributed to foci of cystic degeneration of the prostatic adenomas.

Ten of the technically adequate ta-CEUS studies that were performed immediately post PAE, showed newly appearing, well-defined, ovoid or geographic non-enhancing areas, consistent with infarctions. All infarctions spared the peripheral zone of the gland and had unilateral distribution (at the embolized hemiprostate) in cases of unilateral PAE and bilateral distribution, when they occurred after bilateral PAE. The other 2 ta-CEUS studies showed no significant changes of the prostate enhancement. Regarding the tr-CEUS studies performed 3 days post PAE, 10 of them also detected infarctions in the same patients as the aforementioned ta-CEUS studies. The other 4 tr-CEUS studies showed no visible changes in prostatic enhancement.

Echogenic foci appeared within the majority of the treated prostates post PAE. They were more pronounced

| PV at baseline (ml) min-max (mean±SD.) | ta-US | tr-US |
|--------------------------------------|-------|-------|
| 35-150 (89.8±28.9)                   | 35-145 (86.7±27) |
| PV at 3 mo f-u (ml) min-max (mean±SD.) | 37-130 (71±27.1) | 36-131 (68±27.3) |

PV – prostate volume; 3 mo f-u – 3 months post prostatic artery embolization; SD – standard deviation; ta-US – transabdominal ultrasonography; tr-US – transrectal ultrasonography

Table I. Measurements of PV at baseline and 3 months post prostatic artery embolization PAE.
on the immediate post PAE study, but remained visible in the study 3 days post PAE as well. The number and size of the echogenic foci correlated with the extent of prostatic infarctions; echogenic foci were detected in all 10 prostates which demonstrated infarctions on CEUS and were multiple and larger in cases with extensive infarctions. On the contrary, only 1-2 small echogenic foci appeared in 2 of the 4 non-infarcted prostates. The presence of the echogenic foci was more striking in the unenhanced images, because in the CEUS images the majority of the background echoes were suppressed. Very bright echogenic foci that remained visible in the CEUS images could be differentiated from the microbubbles of the echo-enhancer by observing that the formers were stationary, while the microbubbles were constantly circulating.

At the 3-months follow up, prostatic infarctions had completely disappeared in 4 cases and had become significantly smaller in the rest. There was a strong correlation between ta-CEUS and tr-CEUS regarding the

Fig 1. Sonographic images from a case of successful PAE (unenhanced, reference B-mode images on the left, CEUS images on the right): a) Baseline transabdominal study shows homogeneous enhancement of the enlarged prostate; b) Transabdominal study immediately post embolization shows newly appearing echogenic foci, more prominent on the unenhanced image (arrow). Non-enhancing ovoid infarcts (asterisks) are evident on the CEUS image; c) On a transrectal study 3 days post PAE, the echogenic foci (arrow) are less striking and the presence of infarcts (asterisks) is confirmed; d) On a transabdominal study 3 months post PAE, the extent of infarction (arrow) is diminished and there is considerable shrinkage of the prostate (dotted arrows), with a calculated volume reduction of 32.3%.

Fig 2. Sonographic images from another case of successful PAE (unenhanced, reference B-mode images on the left, CEUS images on the right): a) Baseline transabdominal study shows homogeneous enhancement of the enlarged prostate; b) Transabdominal study immediately post embolization shows that the largest part of the prostate lacks enhancement. There are small areas of residual enhancement at the periphery (arrows); c) Transrectal study 3 days post PAE delineates more clearly the areas of persistent enhancement (arrows); d) On a transabdominal study 3 months post PAE, the infarcts have disappeared and there is a significant shrinkage of the prostate (dotted arrows), with a calculated volume reduction of 52.1%.
measurements of the maximum diameters of the prostatic infarctions, both at the early post PAE and at the 3 months follow-up.

Table II. Prevalence and measurements of prostatic infarcts early post prostatic artery embolization (PAE) and at the 3 months follow-up.

| Infarcts                      | ta-CEUS | tr-CEUS |
|-------------------------------|---------|---------|
| **Early post PAE**            |         |         |
| Present/Absent                | 10/2    | 10/4    |
| Diameter (mm) min-max (mean±SD) | 15-50 (34.1±12.3) | 17-51 (33.8±11.6) |
| **3 months post PAE**         |         |         |
| Present/Absent                | 6/8     | 6/8     |
| Diameter (mm) min-max (mean±SD) | 8-22 (13.6±6.2) | 8-21 (13.8±5.7) |

3 mo f-u – 3 months post prostatic artery embolization; SD – standard deviation; ta-CEUS – transabdominal contrast enhanced ultrasonography; tr-CEUS – transrectal contrast enhanced ultrasonography; SD – standard deviation

Table III. Changes in prostatic volume and relevant infarct measurements.

| PV reduction1 (%) min.-max. (mean±SD) | -5.7-52.1 (19.0±19.9) |
| Infarct Volume2 (ml) min.-max. (mean±SD) | 0-71 (26.4±23.8) |
| Percentage of prostatic infarction3 (%) min.-max. (mean±SD) | 0-82 (29.0±27.1) |

PV – prostate volume; SD – standard deviation; 1Calculated with the formula: [(PV at baseline-PV at 3 mo f-u)/PV at baseline]x100, on the basis of tr-US measurements. A negative value represents an increase rather than decrease in PV post treatment; 2Calculated with the ellipsoid formula, from early tr-CEUS measurements; 3Calculated with the formula: (Infarct Volume/PV at baseline)x100

Fig 3. Sonographic images from a case of failed PAE (unenhanced, reference B-mode images on the left, CEUS images on the right): a) Transabdominal study immediately post embolization shows enhancement of the prostatic adenoma and no infarcts; b) Transrectal study 3 days post PAE confirms the absence of infarcts. Significant intravesical prostatic protrusion is also noted. This patient experienced no symptomatic improvement and no volume reduction was found on reevaluation 3 months post PAE (images not shown).

No infarctions and no prostate shrinkage were observed in the 3 clinical failures of this study (fig 3).

Discussions

To the best of our knowledge, this is the first attempt to study the findings and the potential clinical relevance of early post-interventional CEUS evaluation of PAE. Prostatic infarctions, caused by the acute and irreversible occlusion of the prostatic arterial branches, could be detected by ta-CEUS immediately post completion of the procedure, as well-defined, non-enhancing areas; this feature was more elegantly demonstrated and confirmed 3 days later, by tr-CEUS. CEUS can therefore provide early and convincing evidence on the local effect of the embolization. This is essential for a relatively new treatment alternative like PAE. Indeed, the referring urologists and even some patients could easily appreciate the differences on pre- and post-PAE CEUS images, but not on the complex pelvic arteriograms. Findings similar to ours were described in two previous reports [2,6], in which CEUS was utilized as a complementary modality for prostate imaging at 1, 3 and 6 months post PAE. However, the main purpose of these studies was to evaluate clinical and other outcome parameters of PAE and CEUS findings were not extensively analyzed. Prostatic infarctions were also the key finding of two reports (Kislevzky et al and Frenk et al [3,7]), which had focused
on MRI evaluation (including dynamic, gadolinium-enhanced sequences) of PAE. Infarctions were detected in approximately two thirds of the treated patients, with the morphology and the distribution similar to our results and with the tendency of infarctions to shrink over time.

In our small series, a significant correlation was identified between the presence of prostatic infarctions on early CEUS and the clinical success of the procedure. Early CEUS (even the study performed in the interventional suite) could predict the clinical improvement, which often appeared several days, or weeks post PAE. Infarction visible on early CEUS was also associated with subsequent shrinkage of the gland. The strong association between infarction and clinical benefit and between infarction and prostate shrinkage is also supported by the results of one of the two aforementioned MRI studies, in which MR was performed one month post PAE [7]. Ischemic necrosis appears to play a vital role in the therapeutic effect of PAE. Extensive and irreversible prostatic ischemia eventually results in debulking of the enlarged, adenomatous prostate with the reduction of the mass effect on the prostatic urethra, the increase in urine flow and the improvement of lower urinary tract symptoms [8]. However, mechanisms of action of PAE are far more complicated and visible prostatic ischemia and shrinkage are not prerequisites for clinical success. One of our 11 clinical successes occurred in the absence of infarctions or shrinkage. In the aforementioned study of Frenk et al [3], the proportion of clinical successes in the absence of infarctions was even higher (5/17 patients); others have also reported clinical failures of PAE, despite the effective devascularization and shrinkage of the gland on imaging [9]. It is probable that less severe ischemia (caused, for example, by an incomplete and less aggressive embolization) may not result in detectable infarctions but it may still have a therapeutic effect on BPH through other pathways. These include ischemic apoptosis, androgen-related apoptosis and intraprostatic denervation [8]. With our simple, visual evaluation of CEUS images, we could only detect the sites of complete ischemic necrosis; we could not identify areas of reduced but persistent prostatic perfusion. For the latter purpose, parametric CEUS with dedicated software and with strictly standardized technical parameters is required.

Another potentially valuable result of our study was the strong correlation between the early findings of ta-CEUS and tr-CEUS regarding the presence and the extent of the prostatic infarctions. We recognize that our unidimensional comparison between the two approaches was not very meticulous, and that ta-CEUS images were constantly inferior to tr-CEUS in terms of contrast and spatial resolution. We consider however, that in the clinical setting of PAE, exquisite detail in the depiction of residual enhancement is not as crucial as in other oncologic applications of CEUS. In another study [10], tr-CEUS and ta-CEUS were utilized to study the prostate before biopsy and to produce time-intensity curves and the results of the two approaches were closely comparable. Since ta-CEUS is less invasive and more comfortable than tr-CEUS, it could partially replace the latter in post-interventional imaging of PAE. An additional advantage of ta-CEUS is that it can be applied during the procedure, to provide on-site evaluation of the effect of PAE. If ta-CEUS does not demonstrate the expected parenchymal infarction post PAE, an angiographic re-evaluation may be required, to identify previously undetected or recanalized prostatic arterial branches that require additional embolization.

Several limitations were associated with the present work. The study population was small. Our definition of clinical success was in fact a combination of two different types of clinical improvement; moreover, we did not utilize quantitative parameters (for example, urodynamic ones) to measure the clinical efficacy of PAE. The CEUS results were not correlated with those of MRI, which is considered as the reference imaging modality for the evaluation of PAE. All examinations were performed by the same operator and with the same order (ta-studies first), thus producing a bias in the measurements of tr-US and tr-CEUS. Finally, the measurements were performed at various degrees of bladder distention; it has been demonstrated however, that variations in bladder volume have negligible effect on transabdominal measurements of PV, if bladder volume is within 100-400 ml range [11].

Our initial experience indicates that early post-PAE CEUS is feasible and efficient in the delineation of prostatic infarctions. The latter can be used to document the technical success of PAE and, to some degree, it can also predict the clinical benefit. Future studies should focus on a more detailed, quantitative assessment of the enhancement changes that occur post PAE and on the identification of other, clinically relevant, imaging features.

Conflict of interest: none

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