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CLINICAL INVESTIGATION IMAGING

Effects of Prostatic Artery Embolization on the Dynamic Component of Benign Prostate Hyperplasia as Assessed by Ultrasound Elastography: A Pilot Series

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Abstract

Purpose To determine the effects of prostatic artery embolization (PAE) on prostatic elasticity as assessed by Ultrasound Elastography (US-E), as well as to describe the feasibility and role of US-E as a novel tool in both pre- and post-PAE evaluation.

Materials and Methods This is a prospective, single-center investigation that included eight patients undergoing PAE for treatment of lower urinary tract symptoms (LUTS) attributed to benign prostate hyperplasia (BPH). Baseline and 3-month follow-up evaluations were performed and included prostate-specific antigen (PSA), uroflowmetry, pelvic magnetic resonance imaging and clinical assessment using the International Prostate Symptom Score (IPSS) questionnaire and the IPSS-Quality of life (QoL) item. US-E with measurement of the prostatic Elastic Modulus (EM) was performed before PAE and at 1-month follow-up.

Results After PAE, US-E showed a significant reduction of prostatic EM as assessed in kPa (33.14 vs. 47.24, − 29.8%, $p = 0.002$) and in m/s (3.75 vs. 4.63, − 19.0%, $p < 0.001$). Also, the transitional/peripheral zone ratio was significantly reduced by 45.36% (0.53 vs. 0.97, $p < 0.05$). All eight patients presented with significant LUTS improvement after PAE ($p < 0.05$ for IPSS, QoL, prostate volume, peak urinary flow rate and PSA).

Conclusions Findings described in this study suggest that PAE significantly reduces prostatic EM, leading to a positive effect on BPH dynamic component related to prostatic elasticity. Also, it features US-E as an additional tool for pre- and post-PAE evaluation, describing a novel indication for this technology.

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Keywords Benign prostatic hyperplasia · Prostate artery embolization · Lower urinary tract symptoms · Ultrasound Elastography

Introduction

Prostatic artery embolization (PAE) has recently been described as a minimally invasive option for treatment of LUTS attributed to BPH, leading to prostate volume reduction and clinical improvement, with low incidence of complications and same-day hospital discharge [1–13]. Although studies have demonstrated prostate volume reduction as an important predictor of clinical success after PAE, patients with less pronounced shrinkage still experience LUTS improvement [14]. This suggests that PAE could lead not only to prostate volume reduction, but also to an improvement of the alpha-adrenergic mediated dynamic component of BPH.

These possible effects of PAE on prostatic tone inspired the investigation of prostatic elasticity using ultrasound (Ultrasound Elastography—US-E), a method which is already employed to determine the elasticity of many organs by shear wave velocity (SWV) measurements. In fact, a few studies investigated US-E as a diagnostic tool for BPH and prostate cancer [15–19]. Zhang et al. [18] in a study that included 55 patients demonstrated a strong correlation between transitional zone elastic modulus (EM) assessed by SWV measurement and the severity of bladder outlet obstruction (BOO), where SWV $\geq$ 32.4 kPa predicted BOO with a 96.7% sensibility and 72.7% accuracy. Moreover, patients with "severe BOO" had higher mean transitional zone SWVs when compared to "slight to moderate" and to "no BOO" (36.3 kPa vs. 30.6 kPa vs. 27.7 kPa, $p < 0.001$), reflecting the higher prostatic stiffness caused by BPH.

The objective of this study is to determine the effects of PAE on prostatic elasticity as assessed by US-E, as well as to discuss possible implications of such findings in clinical practice.

Materials and Methods

This is a single-center, open-label prospective investigation that included eight patients who underwent PAE to treat LUTS attributed to BPH between February and October of 2018. The institutional review board approved the study protocol, and all patients signed informed consent for the procedure.

Inclusion criteria:

1. Patients with LUTS refractory or intolerant to pharmacological treatment (α-1-adrenergic receptor antagonist and/or 5-α-reductase inhibitor).
2. IPSS > 7 (moderate to severe symptoms).
3. Prostate volumes ranging from 40 to 200 cm^3.

Exclusion criteria:

1. Histological diagnosis of prostate cancer.
2. Acute urinary tract infection.
3. Patients with urinary retention and indwelling catheters.
4. Neurogenic bladder disorders.
5. Creatinine level > 2.0 mg/dL.
6. Previous history of pelvic radiotherapy or surgery.

Baseline and 3-month follow-up evaluation included prostate-specific antigen (PSA) testing, uroflowmetry and pelvic MRI. Prostate US-E with measurement of SWV values was performed before PAE and at the 1-month follow-up evaluation. Patients' clinical symptoms were assessed using the IPSS questionnaire and the IPSS-QoL item, for which responses range from "6, Terrible" to "0, Delighted." All patients were using α-1-adrenergic receptor antagonist ± 5-α-reductase inhibitor at the time of PAE and maintained the medications until the 1-month US-E re evaluation.

Ultrasound Elastography Protocol

Prostate US-Es were performed before PAE and at 1-month follow-up for each patient (Fig. 1), using a dedicated device (Toshiba i800, Toshiba Medical Systems Corporation, Japan) with an endocavitary probe (11C3), by a transrectal approach. All examinations were performed by an experienced diagnostic Radiologist (23 years), with specific training in US-E.

Mean SWV values were obtained including the whole transitional zone, bilaterally, at the middle third of the prostate (Fig. 2). Sample SWV values were obtained using a 0.5 cm^2 region of interest (ROI) at the right periurethral transitional zone and at the adjacent peripheral zone (Fig. 3), and the ratio between them was calculated. SWV values were recorded in both meter/second (m/s) and Kilopascal (kPa). Areas of calcification were avoided during the ROI placements.

PAE Technical Protocol

The PAE procedures were performed in the interventional radiology suite with Innova DSA (GE Healthcare, Chalfont St. Giles, Buckinghamshire, UK), using nonionic contrast medium (320 mgI/mL iodixanol [Visipaque; GE

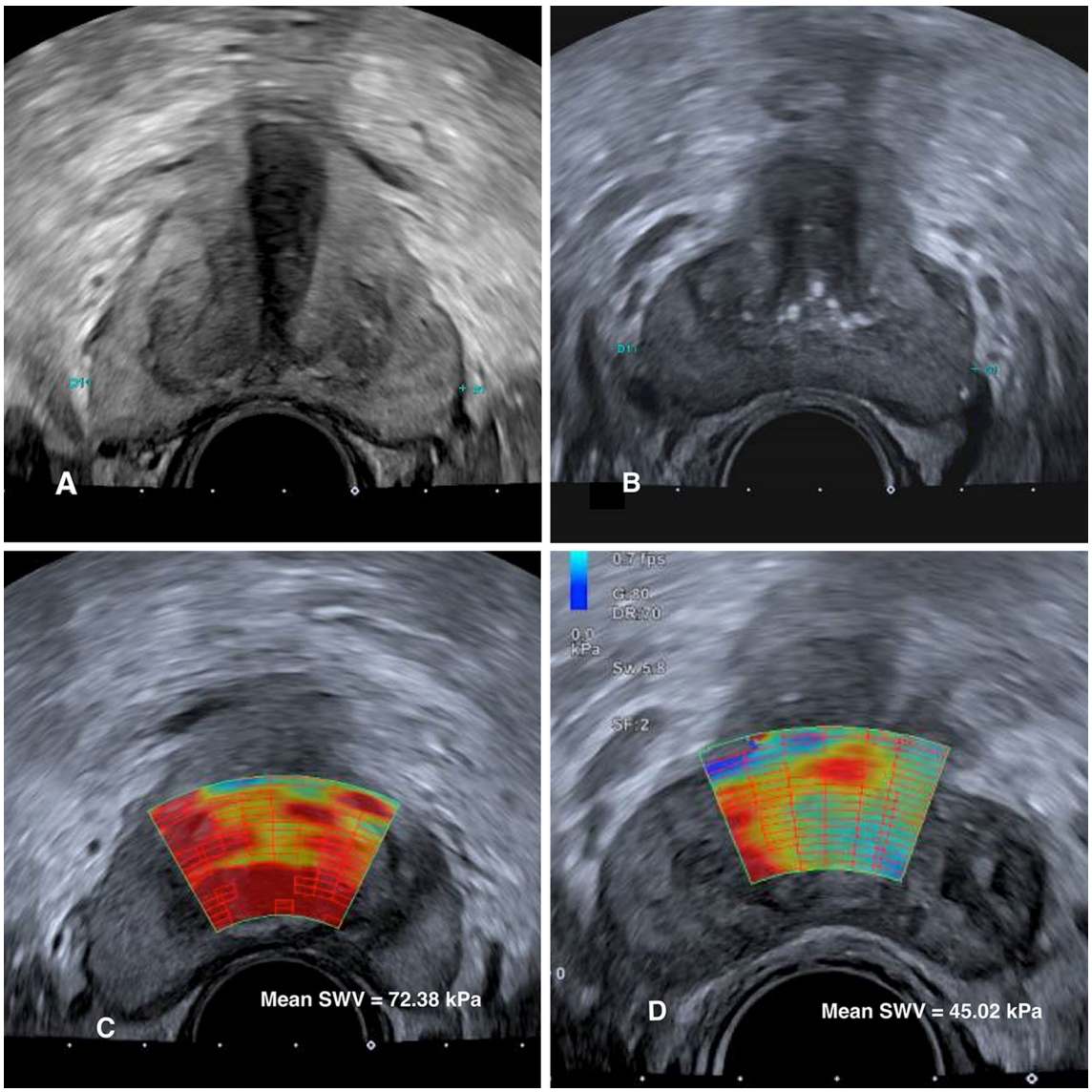

Fig. 1 Pre-PAE (**A**) and 1-month follow-up (**B**) transrectal ultrasound showing volumetric reduction of the gland, notably of the transitional zone. (**C**, **D**) Ultrasound Elastography demonstrating reduction of prostatic elastic modulus after PAE

Healthcare, Cork, Ireland]), through a unilateral femoral approach, according to previously described methods [20, 21].

The goal of the procedure was embolization of all feeding branches to the prostate, bilaterally. Selective catheterization of the right and left prostatic arterial branches was performed using a 2.0F microcatheter (Progreat®, Terumo, Tokyo, Japan), followed by embolization with 300–500 μm tris-acryl Embosphere® Microspheres (Biosphere Medical, Roissy, France) until complete stasis. Intra-procedure findings were confirmed by Cone-Beam CT (CBCT).

Patients were discharged from the hospital 3–6 h after PAE.

Statistical Analysis

All statistical tests were performed using GraphPad Prism 3.0 (San Diego, CA, USA). Baseline and follow-up values for IPSS, QoL, peak urinary flow (Qmax), prostatic volume (PV), PSA and SWV (in m/s and kPA) were described as means with accompanying standard deviations. Values were compared between time points using paired *t*-tests. The significance level for all statistical tests was defined as a two-sided *p* value of 0.05 or less.

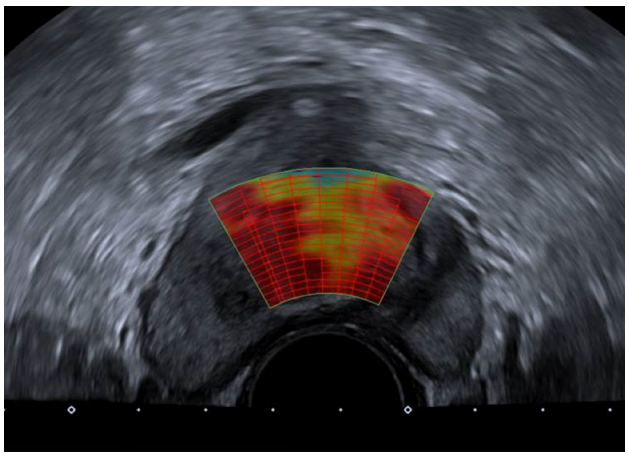

Fig. 2 Mean transitional zone SWV assessed by Ultrasound Elastography

Results

At 3-month follow-up, all patients presented with significant improvement of clinical, urological and radiological outcomes ($p < 0.05$ for IPSS, QoL, Qmax, PV and PSA, Table 1). There was no LUTS recurrence or clinical failure in this cohort.

Regarding US-E results, a significant reduction of transitional zone EM was observed as assessed by mean SWV in kPa (33.14 vs. 47.24, − 29.8%, $p = 0.002$) and in m/s (3.75 vs. 4.63, − 19.0%, $p < 0.001$). Also, the transitional/peripheral zone ratio was significantly reduced (0.53 vs. 0.97, − 45.36%, $p < 0.05$). There was no significant change in peripheral zone EM assessed in m/s (6.43 vs. 6.23, − 3.1%, $p = 0.62$). In one patient with a very enlarged prostate, attenuation of the shear wave in the anterior segment of the transitional zone was observed (Fig. 4). Despite this, his US-E results were not excluded from the statistical analysis. Baseline and follow-up data are summarized in Table 2.

In this cohort, no minor or major complications were observed.

Discussion

In the last decade, PAE has become an important minimally invasive alternative to the surgical procedures for the treatment of LUTS related to BPH, with multiple reports

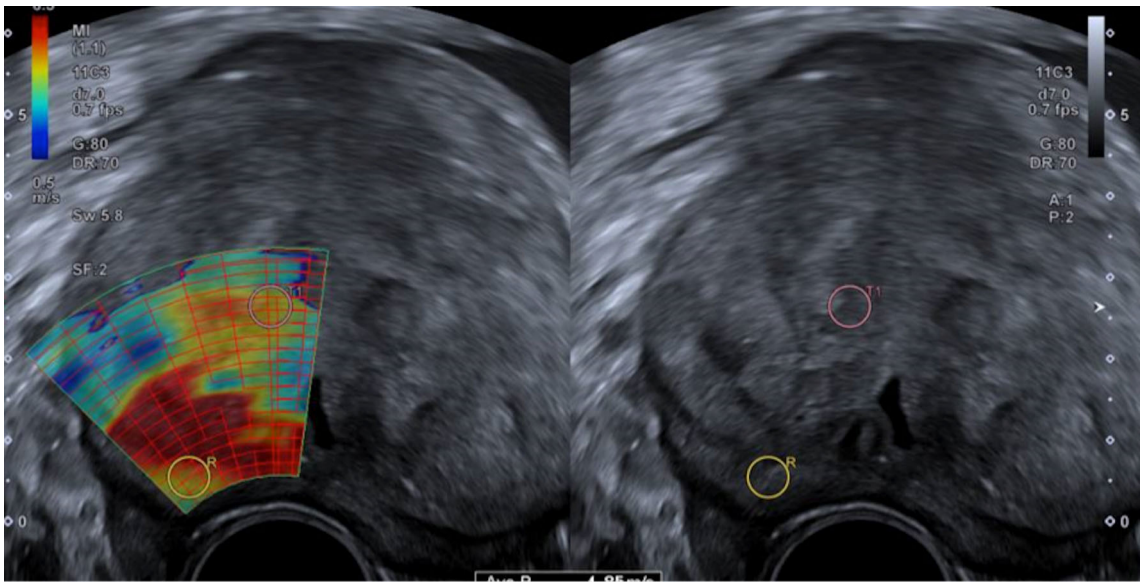

Fig. 3 Sample SWVs obtained at the right periurethral transitional zone (T1) and at the adjacent peripheral zone (R) [(Circles—0.5 cm^2 regions of interest (ROIs)]

Table 1 Baseline characteristics and 3-month clinical outcomes (mean ± SD)

	Baseline	3-month FU*	Change (%)	*p* value
IPSS	19.25 (± 5.51)	6.87 (± 3.89)	− 12.38 (− 64.31%)	< 0.0001
QoL	4.00 (± 0.71)	1.25 (± 0.83)	− 2.75 (− 68.75%)	< 0.0001
Qmax (mL/s)	7.63 (± 4.22)	13.56 (± 4.60)	+ 5.93 (+ 77.7%)	< 0.001
Prostate volume (cm^3)	85.89 (± 43.65)	59.60 (± 25.43)	− 26.29 (− 30.6%)	< 0.001
PSA (ng/dL)	6.64 (± 7.58)	2.11 (± 1.31)	− 4.53 (− 68.22%)	0.04

**FU*, follow-up

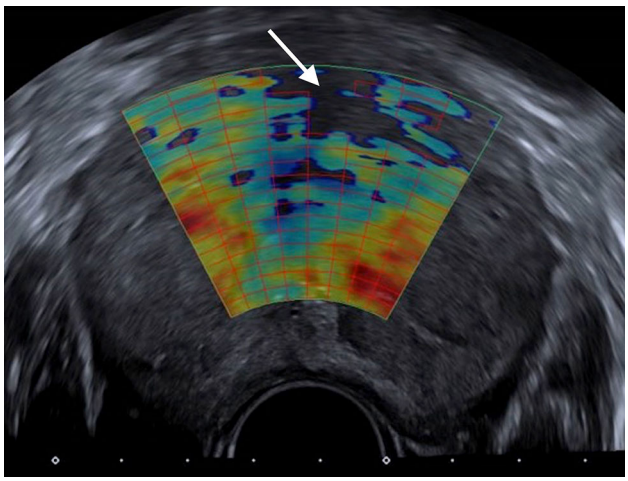

Fig. 4 Attenuation of the shear wave in the anterior segment of the transitional zone in a very enlarged prostate (194.5 cm^3) (arrow)

confirming its efficacy and safety [1–13]. PAE causes occlusion of the microvascular compartment within the transitional zone, leading to coagulation necrosis of the BPH nodules, volume reduction and, ultimately, amelioration of the static component of BPH related to the extrinsic compression of the prostatic urethra. For this reason, prostate volume reduction has been considered as an important predictor of clinical outcomes after PAE [14].

BPH pathophysiology, however, includes not only the growth of benign nodules in the periurethral transitional zone, leading to bladder outlet obstruction (BOO)—the *static component*. There is also an increase in stromal smooth muscle tone—the *dynamic component*—which plays an important role, contributing to the increase in prostate stiffness seen in BPH [22, 23]. In fact, prostatic volume itself does not correlate directly to the severity of symptoms [24].

Indeed, in several cases, improvement of LUTS occurs even in patients that present with limited volume reduction after PAE, being possible that embolization also works by improving the dynamic component of BPH, related to prostate and bladder neck elasticity. In addition to that, it was noted in clinical practice that prostate seems to feel softer during digital rectal examination after embolization [21]. This hypothesis is corroborated by the findings of this study, which demonstrated a significant reduction of the prostate EM after PAE as assessed by the mean transitional zone SWV measurement in both m/s (− 19.0%, $p < 0.001$) and kPa (− 29.8%, $p = 0.02$) and also by the transition/peripheral zone ratio (− 45.35%, $p < 0.05$).

The dynamic component of BPH is related to the activation of the alpha-receptors within the prostate and bladder neck, leading to an increase in the overall stiffness of the gland and functioning as a non-obstructive obstacle to the urinary flow through the prostatic urethra [23]. The alpha-activation happens in the presence of sympathetic mediators reaching the gland via local microcirculation [25], a pathway that is occluded during PAE. Thus, embolization can block the influx of such mediators to the prostate, leading to overall hypo-activation of the alpha-receptors. In addition to that, it has been demonstrated that PAE leads to ischemic necrosis of transitional zone tissue [26], which could reduce alpha-adrenergic receptors density, also contributing to reduction of prostate tone.

The findings described herein may also have important impact on clinical practice regarding the minimally invasive management of patients suffering from LUTS attributed to BPH. With further study, baseline EM may be demonstrated to be a predictor of outcomes after PAE, improving patients' selection and optimizing clinical results. In addition, US-E could be considered as a more accessible option than MRI as a pre- and post-PAE imaging examination, or even be performed in patients with contraindications to MRI, providing important information regarding anatomical and functional aspects of BPH. BPH evaluation using US-E needs further research, but certainly has the potential to become an important prognostic tool.

Finally and equally important, the characterization of PAE effects on the dynamic component of BPH creates an argument to its use as an alternative option for patients currently in treatment with α-1-adrenergic receptor antagonists. Although acting by different mechanisms—the medication competitively inhibits postsynaptic receptors in prostatic stromal and bladder neck tissues [25]—both PAE and α-1-adrenergic receptor antagonists lead ultimately to reduction of the sympathetic prostatic tone. Previous non-controlled reports demonstrated better outcomes for PAE when compared to those described for α-1-adrenergic receptor antagonists, which typically improve IPSS in 4–6 points and Qmax in 2.0–2.5 mL/s [27]. In this study, IPSS

Table 2 Baseline characteristics and 1-month elastographic outcomes (mean ± SD)

	Baseline	1-Month FU*	Change (%)	*p* value
Transition zone SWV (kPA)	47.24 (± 17.42)	33.14 (± 11.94)	− 14.1 (− 29.8%)	0.002
Transitional zone SWV (m/s)	4.63 (± 0.91)	3.75 (± 0.84)	− 0.88 (− 19.0%)	< 0.001
Peripheral zone SWV (m/s)	6.43 (± 1.57)	6.23 (± 1.66)	− 0.20 (− 3.1%)	0.62
Transitional/peripheral zone ratio	0.97 (± 0.82)	0.53 (± 0.34)	− 0.44 (− 45.36%)	< 0.05

**FU*, follow-up

improved 12.38 points after PAE, while Qmax was increased by 5.93 mL/s ($p < 0.001$ for both). Nevertheless, no randomized controlled trials comparing these treatment options were published so far.

Main weaknesses of this study are the small sample size and short follow-up period. Long-term investigations may clarify the possibility of a re-increase in prostate stiffness over time during PAE follow-up, since re-vascularization was already described to be an issue [28]. Also, histological assessment would help to confirm some of the hypothesis formulated in text. Technically, elasticity of transitional zone appeared to be very heterogeneous, making the analysis based on 0.5 cm ROI less appealing; to mitigate this issue, the whole transitional zone assessment was performed in every patient and could be considered a more reliable parameter. Finally, in very large prostates, it was observed attenuation of the shear wave in the anterior segment of the transitional zone (Fig. 4), possibly affecting the results in these patients.

In conclusion, findings described in this study suggest that PAE significantly reduces prostate EM, resulting in elasticity improvement after the procedure. Also, it demonstrates the feasibility of US-E as a tool for pre- and post-PAE evaluation, describing a novel indication for the use of this technology, which is capable of providing important anatomical and functional information of the BPH disease.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The institutional review board approved the study protocol.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

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