Is there any potential role for the elastography on the evaluation of clinical success of prostate artery embolization (PAE) on the treatment of benign prostatic hyperplasia (BPH)?

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Abstract
Benign prostatic hyperplasia (BPH) is a very common condition in the male. It typically occurs in the sixth and seventh decades. Actually BPH is a histologic finding that becomes a clinical entity if and when it is associated with subjective symptoms. Not all men with histologic BPH will have significant lower urinary tract symptoms (LUTS) and other men who do not have histologic BPH will develop. In fact LUTS are also present in other diseases such as infection and cancer of the prostate, urethral stricture, etc. Traditionally, symptomatic benign prostatic hyperplasia is treated with either medical therapy or surgery. Among prostate-directed treatment modalities, prostate artery embolization (PAE) is the less invasive non pharmaceutical treatment. Initial studies showed that PAE led to reduction of the prostatic volume, symptom remission and improvements in quality of life. As a relatively new procedure, few data exist to clearly determine the exact mechanism(s) by which PAE achieve the above results.

Introduction: Pathophysiology of BPH
BPH is a histologic diagnosis characterized by proliferation of the cellular elements of the prostate. This involves both stromal and epithelial cells, resulting in the formation of large, fairly discrete nodules in the transition zone of the prostate [1]. The aetiology remains somehow unclear. Currently is considered as being a normal part of the aging process in men caused by changes in intra-prostatic hormone balance (either by higher proportion of estrogen within the prostate or accumulation of high levels of dihydrotestosterone that both increases the activity of substances that promote prostate cell growth). Interactions between growth factors and steroid hormones may ulteriorly al-

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ter the balance of cell proliferation versus cell death to produce BPH [2]. Alongside the age related hormonal alterations, evidence suggests that, failure in the spermatic venous drainage system in BPH patients results in increased hydrostatic pressure and local testosterone levels elevation (more than 100 fold above serum levels) [3]. Both the glandular epithelial cells and the stromal cells (including muscular fibers) undergo hyperplasia [4]. Given that BPH represent an increase in the number of cells rather than a growth in the size of individual cells, only 50% of individuals with histologic findings have clinical enlargement of prostate. Moreover, correlation among histology, clinical enlargement of prostate and symptoms is controversial since less than 50% of BPH patients with enlarged prostate have LUTS [5]. This is partially attributed to the nature of symptoms: Obstructive symptoms are thought to result either from mechanical obstruction due to glandular enlargement, or from dynamic obstruction secondary to contraction of the smooth muscles of the prostate, urethra and bladder neck. As stromal hyperplasia develops, the number of alpha-1 adrenoceptors increase. Subsequently, a sympathetic nervous system mediated overstimulation occurs, resulting in dynamic obstruction. Storage symptoms appear to be caused by detrusor instability related to detrusor muscle changes in response to obstruction, such as bladder wall hypertrophy and collagen deposition in the bladder [6]. Increased tonality of the muscular tissue of the prostate -as a result of fluid secretion obstruction due to BPH- lead to progressive fibrosis of muscular tissue and accumulation of fluid that causes for the expanding of the prostate in benign prostatic hyperplasia[7].

Of note, LUTS are also present in other diseases such as infection and cancer of the prostate, urethral stricture, etc. Although bladder irritation is bothersome, chronic bladder outlet obstruction may lead to serious complications such as renal insufficiency, recurrent urinary tract infections and gross hematuria and bladder calculus formation as well [8]. Symptoms burden varies. Mild symptoms usually do not require treatment however moderate and severe symptoms could be treated with either medical therapy or surgery. Currently prostatic arterial embolization (PAE) was emerged as a feasible procedure to treat lower urinary tract symptoms associated with BPH. PAE is the less invasive non pharmaceutical treatment. Initial studies showed that PAE led to reduction of the prostatic volume, symptom remission and improvements in quality of life However, as a relatively new procedure, few data exist to clearly explain the exact impact of PAE on the BPH pathophysiology. In the present article we aim to investigate the possible mechanism(s) by which PAE reduces BPH induced LUTS.

**Material and Methods**

A search was performed in MEDLINE, NCBI, Pubmed, Cochrane Library and other electronic libraries using the following terms: “benign prostatic hyperplasia”, “lower urinary tract symptoms”, “prostate enlargement”, “prostate” , “steroid hormones” , “symptom remission” , “prostatic volume” in combination with the keywords: “prostate artery embolization”, “prostate pharmaceutical treatment”, “prostate surgery”. The articles selected were checked for the relevancy of their content to the discussed subject. The bibliographic information in the selected articles was checked for relevant publications that had not been included in the original search.

**Results**

**Current BPH treatment options**

Medical treatment includes α1-adrenoceptor antagonists (α1-AR inhibitors), inhibitors of 5a-reductase, combination of the above, phosphodiesterase type 5 inhibitors (PDE5 inhibitors) combination of α1-blocker with PDE5 inhibitor and combination of α1-blocker with anticholinergic agent. The mechanism of action of the abovementioned four factors varies: α1-AR inhibitors cause urethral dilation and prostatic smooth muscle relaxation by blocking the binding of norepinephrine to the smooth muscle receptors [9]. On other hand, 5a-reductase inhibitors (SARIs) are compounds that block the conversion of testosterone to dihydrotestosterone (DHT). DHT initiates transcription and translation promoting thus cellular growth and BPH development. Since 5α-reductase inhibition
lead to 60%-95% decrease in circulating DHT, shift the imbalance between growth and apoptosis in favour of cellular death and subsequently induce prostatic volume decrease [10].

Anticholinergic medications inhibit the stimulation of the smooth muscle of the bladder by the action of acetylcholine on muscarinic receptors reducing thus the BPH related irritative urinary symptoms [11]. Finally, PDE5 inhibitors increase levels of nitric oxide (NO) repairing thus the associated with BPH decrease in NO-mediated relaxation of prostate smooth muscle [12].

Surgery (transurethral resection or open prostatectomy) is the appropriate treatment option for patients with moderate to severe LUTS, urinary retention, recurrent urinary tract infections and significant residual urine after voiding and pathophysiological changes of the kidneys, ureters, or bladder as well [13]. Both transurethral resection and open prostatectomy reduce prostatic volume nevertheless urethral reformation after prostate surgery also occurs.

Minimally Invasive Surgical Techniques include transurethral microwave therapy (TUMT), transurethral needle ablation (TUNA), laser resection/ablation (LRA), transurethral ethanol ablation (TEAP), and high intensity frequency ultrasound (HIFU) [14]. The abovementioned techniques reduce prostatic volume. LRA with Holmium provide comparable results to TURP (in IPSS's and flow rates), while having lowing complication rates. Randomized, comparative trials between TUMT and TUNA versus TURP show symptom scores to be comparable, though flow rates were clearly superior for TURP [14].

**PAE in the treatment of BPH related LUTS: Criteria of clinical success**

It is less than a decade that PAE was tested in the treatment of BPH induced LUTS. Initial experience showed promising results in terms of reduction of the prostatic volume, symptom remission and improvements in quality of life. However, no generally accepted definition for clinical success exists. In fact, principal outcome assessment varies among studies and could be either objective or subjective, laboratory, clinical or both. For example, regaining the ability to urinate after PAE is a measurable size whereas questionnaire-based self-reported improvement of both urination and sexual function and QoL as well is not. Furthermore, as long as the exact mechanism by which PAE affects BPH induced LUTS remains unclear, reduction in prostate volume and serum PSA value may not be the most adequate outcome measures. In fact, clinical success—in terms of IPSS and Qmax—is not always analogous to prostate volume reduction. Moreover, the reduction on prostate volume occurs progressively and stabilized within six months of the procedure. Yet, up to 20% of patients undergoing PAE show no prostate volume reduction 3 months after the procedure [15].

A small MRI study showed that reduction of the prostate volume after embolization was significant only in patients with infarcts [16]. In this study infarcts were seen in only 70.6% of the subjects, exclusively in the central gland. However, a retrospective study showed that prostatic volume decrease occurs in both central and peripheral zones [17], a fact suggesting disproportion between infarcts and reduction of the prostate volume. Although, a small MRI study proposed infarcts to be a good predictor of clinical success after PAE in patients with AUR secondary to BPH [18], it seems that it is not the case.

A significantly high PSA elevation occurs in the 24 hours after PAE. During follow-up, mean PSA decreases to a level significantly lower than at baseline. This is suspected to result from prostate inflammation and ischemia due to embolization and suggests prostate cellular apoptosis after PAE [19]. However, no statistically significant correlation was detected between PSA level 24 hours after PAE and prostate volume reduction at 3 months of follow-up [20]. In contrast, a statistically significant negative correlation between PSA level elevation 24 hours after PAE and IPSS decrease at 3 months of follow-up was reported [31]. It should be mentioned that other conditions that can increase PSA levels such as pre-existing inflammation, pre-treatment prostate manipulations (e.g. catheterization) and prostate size may bias this association. Moreover IPSS has inadequate sensitivity and specificity to be used as a standalone tool in the evaluation of clinical success of a new method such as PAE. Although, a study proposed PSA elevation after PAE to be a prognostic factor for predicting patient response to PAE [31], more research is needed in order to confirm this suggestion.

In fact, uncertainty regarding the role of pre-treatment prostatic volume in the successfulness of PAE exists. Bagla et al., performed an analysis on 78 consecutive patients undergoing PAE, comparing pros-
tate volume groups (group 1 < 50 cm³; group 2, 50-80 cm³; group 3 >80 cm³) at baseline and follow-up to assess for differences in outcomes of American Urological Association (AUA) symptom index, quality of life (QOL)-related symptoms, and International Index of Erectile Function (IIEF). According to their result no statistically significant differences in the above parameters was found between groups [21]. Other authors suggest that patients with a smaller prostate (i.e., volume < 30 cm³) should excluded because PAE is believed to work based on prostate volume reduction, which will be more limited in patients with almost normal sized prostates [22]. Interestingly, Little et al., found a statistically significant reduction in prostate volume following embolization with a median reduction of 34% (30-55) in the group of patients with adenomalous-dominant BPH (AdBPH), compared to a mean volume reduction of 22% in the non-AdBPH group. IPSS and QOL score significantly improved in the AdBPH group while there was no deterioration in sexual function in either group post-PAE [23].

**Discussion**

The abovementioned findings may indicate a greater impact of PAE induced ischaemia in the adenomalous than in the stromal element of the prostate gland. However, as clinical effect occurs progressively and stabilized within six months it is possible that PAE resolves both mechanical and dynamic obstruction. This hypothesis along with the clear evidence on the superiority of PAE over medical monotherapy (either 5ARIs or a-blockers) provided the rationale of (PAE) in the treatment of symptomatic benign prostatic hyperplasia in a more systematic fashion. The exact mechanism(s) by which PAE resolves mechanical obstruction is the shrinkage of the enlarged prostate gland as a result of PAE induced ischemic infarction. Regarding the effects of PAE by which relaxes the increased prostatic smooth muscle tone, several potential mechanisms have been proposed. Among them are the reduction of the number and density of a1-adrenergic receptor in the prostatic stroma following as ischemia-induced apoptosis, apoptosis enhanced by blockage of androgens circulation to the embolized prostate, secondary denervation following PAE, and potential effect of nitric oxide pathway immediately after embolization [24]. However, an alternative mechanism that resolves dynamic obstruction in a way quite similar to that of surgery is not to be excluded.

As shown in canine prostate model, at 2 weeks after surgery, the wound response gradually changes into a regenerative phase characterized by marked proliferation of the epithelial glandular elements with notable squamous metaplasia. At 3 weeks, inflammatory cell infiltration is gradually replaced by granulation tissue and re-epithelialization is essentially complete. At 4 weeks, gradual decrease in squamous metaplasia occurs and the granulation tissue is replaced by well-organized underlying connective tissue. Along with the reconstruction of the prostate urethra a subsequent stromal relaxation also occurs.

Current knowledge on the histology of prostate tissue following PAE for the treatment of benign prostatic hyperplasia is extremely limited. Camara-Lopes et al., described early prostate tissue histology changes after PAE. Along with embolic material (bright eosin-red spheroids filling the vessel lumens) they observed also areas of ischemic necrosis. The transition zone between necrotic and normal prostate tissue was characterized by inflammatory reactions containing macrophages. The two areas were furtherly delimited by ribbons of neutrophils, lymphocytes and proliferated fibroblasts. Nodular fibrosis with hyalinization as a consequence of the healing process was present in some areas associated with squamous metaplasia of the epithelium lining the surrounding glands. The remaining 95% of the prostate tissue exhibited, glandular and stromal hyperplasia, as well as mild, nonspecific chronic prostatitis [25]. Actually there are no studies examining long term prostate tissue histology changes after PAE. Given that PSA values decreases to a level significantly lower than at baseline but no ejaculation disorders occur it could be assumed that prostate gland return in fully functional state after PAE. As a matter of fact, metaplasia that occurs in response to necrosis and inflammation may represent an adaptive substitution of cells that are sensitive to stress by cell types better able to withstand the adverse environment and is reversible. On the other hand, the regained ability to urinate after PAE may be associated with changes in stromal elements. Because fibroblasts are typically activated following injury and are the main producers of extracellular matrix proteins, their role as reparative cells is widely recognized. Although the post-PAE heal-
Η καλοήθη υπερπλασία του προστάτη είναι μια πολύ κοινή κατάσταση στους άνδρες κυρίως δε εμφανίζεται στην έκτη και την έβδομη δεκαετία της ζωής. Στην πραγματικότητα αποτελεί ένα ιστολογικό εύρημα που γίνεται κλινικά οντότητα και όταν συνδεθεί με υποκειμενικά συμπτώματα. Ωστόσο, περίπου το 50% των άνδρων με ιστολογική καλοήθη υπερπλασία του προστάτη εμφανίζει συμπτωματική κατάσταση ενώ και άτομα που δεν έχουν καλοήθη υπερπλασία θα αναπτύξουν παρόμοια συμπτωματολογία. Παραδοσιακά, τα συμπτώματα που συνδέονται με την καλοήθη υπερπλασία του προστάτη αντιμετωπίζονται με προστατοκεντρικές θεραπείες φαρμακευτικές ή χειρουργικές. Ο εμβολισμός των αρτηριών του προστάτη είναι η λιγότερο επεμβατική μη φαρμακευτική θεραπεία. Η μέθοδος αυτή έχει χρησιμοποιηθεί ήδη από την δεκαετία του 1970 στην αντιμετώπιση της μετεγχειρητικής και νεοπλασματικής αιμορραγίας. Αργότερα δοκιμάστηκε ως μέσο τοπικής χημειοθεραπείας στον τοπικό και προχωρημένο καρκίνο του προστάτη, ενώ έχει αναφερθεί καθετηριασμός των αρτηριών του προστάτη για εφαρμογή σκληροθεραπείας στην αντιμετώπιση των καλοήθων όγκων του οργάνου. Είναι λιγότερο από μια δεκαετία που η μέθοδος αυτή δοκιμάστηκε στην αντιμετώπιση των ενοχλημάτων ούρησης που σχετίζονται με την καλοήθη υπερπλασία του προστάτη. Αρχικές μελέτες έδειξαν ότι επιτυγχάνεται μείωση του όγκου του προστάτη, ύφεση των συμπτωμάτων και βελτίωση της ποιότητας ζωής. Ως μια σχετικά νέα διαδικασία, υπάρχουν λίγα δεδομένα για να προσδιοριστεί σαφώς ο ακριβής μηχανισμός/μηχανισμοί με τον οποίο επιτυγχάνεται τα παραπάνω αποτελέσματα ούτε εχει προσδιοριστεί η ιδανική μέθοδος ανάδειξης αυτών.

**Περίληψη**

Ελαστογραφία για την επιμόρφωση μετά τον εμβολισμό των αρτηριών του προστάτη, έχει χρησιμοποιηθεί για την εκτίμηση της δυνατότητας μείωσης της ουροφόρης οδού, των συμπτωμάτων και του όγκου του προστάτη. Ο εμβολισμός των αρτηριών του προστάτη είναι η λιγότερο επεμβατική μη φαρμακευτική θεραπεία. Η επιρροή της ελαστογραφίας στην αντιμετώπιση των καλοήθων όγκων του οργάνου είναι λίγο και αρκετά επαρκής για να συμβάλει στη μείωση της ουροφόρης οδού και των συμπτωμάτων. Τον χρόνο κατά την οποία περιμένεται η εμφάνιση των συμπτωμάτων, η ελαστογραφία μπορεί να χρησιμοποιηθεί για την εκτίμηση της αντιμετώπισης και της δυνατότητας μείωσης της ουροφόρης οδού. Με την ελαστογραφία, είναι δυνατή η εκτίμηση της δυνατότητας μείωσης της ουροφόρης οδού και της βελτίωσης της ζωής στοιχείο σημαντικό για την αντιμετώπιση των καλοήθων όγκων του προστάτη.

**Λέξεις ευρετηριασμού**

- καλοήθη υπερπλασία του προστάτη
- συμπτώματα κατώτερης ουροφόρου οδού
- ύφεση συμπτωμάτων, όγκος του προστάτη
- εμβολιασμός της προστάτης αρτηρίας
- αρτηριακή αγωγή του προστάτη
- χειρουργική της προστάτη
- σκληροθεραπεία
- ελαστογραφία
- στερεόμετρα
- σιωπηρή ελαστογραφία
- καλοήθης υπερπλασία του προστάτη
- αρτηριακή αγωγή του προστάτη
- αναπνευστική απίλειψη
- απώλεια ουροφόρης οδού
- ελαστογραφία
- ελαστογραφία

**Conclusion**

PAE is a safe and efficient method for the treatment of both mechanical and dynamic component of bladder outlet obstruction in patients with BPH. Current imaging outcome measures are consistent with clinical ones in the group of patients with adenomatous-dominant BPH while are inconsistent in patients with small sized adenomas. Elastography may be useful for the evaluation of PAE outcome in these patients while may shed light on the pathophysiology of BPH and inspire new options and novel techniques for both treatment and follow up. [1]

**Conflicts of interest**

The author declared no conflict of interest.
Elastography for PAE evaluation, p. 28-33

References