Obstruction-induced pathological alterations within the urinary bladder due to Benign Prostate Hyperplasia (BPH)
A review of the literature

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Summary
Introduction
Benign prostatic hyperplasia (BPH) is a frequent cause of Bladder Outlet Obstruction (BOO) and Low Urinary Tract symptoms (LUTS). BPH process induces functional, biochemical and morphological alterations, in order for the urinary bladder to maintain a normal functionality. There is substantial evidence that detrusor blood flow significantly decreases in the presence of BOO. This review addresses the bladder response to BOO and focuses on the alterations and biochemical adaptability of the bladder wall in the presence of hypoxia.

Methods
A literature review of published articles has been performed, including both in vivo and in vitro studies on human and animal tissue.

Results
In the presence of obstruction and hypoxia, muscle enlargement and collagen deposition comes upon, mitochondria sustain damage, mitochondrial DNA deletions and decrease mitochondrial enzyme activity occur leading to a decreased oxidative metabolism and ATP synthesis. Anaerobic metabolism and probably glycogen deposit increase, in order for the muscle cells to find alternative energy supplies. As a result, lactic acid due to the anaerobic metabolism accumulates in the smooth muscle causing contractile dysfunction. Furthermore, hypoxia induces bladder wall denervation and reduces cholinergic nerve density.

Conclusion
BOO is a key factor in the aetiology of LUTS/BPH. Obstruction is associated with a variety of morphological, contractile and biochemical changes within the bladder.

Key words
Benign prostatic hyperplasia; bladder outlet obstruction; urinary bladder; detrusor muscle.

Introduction
BPH affects 50% to 90% of men between 50 and 85 years of age¹. It is a common disorder of the male urogenital tract typically accompanied by LUTS (hesitancy, straining, weak urine flow, frequency, nocturia and urgency)². BPH-related symptomatology is attributed to obstructed outflow (BOO), which results from either prostate enlargement (static component) and/or increased α-adrenergic activity at the level of bladder neck and prostatic urethra (dynamic component)³⁴. BOO has been shown to be associated with a variety of morphological, contractile and biochemical changes within the bladder in both experimental and clinical studies. In general, the bladder modifies its structure to compensate the increased resistance to flow. Furthermore, it is known that in partial outlet obstruction significant hypoxia ensues because of the high resistance to flow and consequent high intravesical pressure. The present review addresses current data on the response of the bladder to BOO particularly
focusing on the bladder wall alterations and biochemical adaptability in the presence of hypoxia.

Methods
For this publication, both in vivo and in vitro studies on human and animal tissue were used to estimate the consequences of outlet obstruction on the bladder wall. A search of the PubMed using the terms “Benign Prostate Hyperplasia”, “Bladder Outlet Obstruction”, “bladder hypoxia” and “detrusor ischemia” was conducted. The search was limited to the period 1980-2013. Forty-six manuscripts were selected for their relevance to the subject of the review.

Results
Bladder response to outlet obstruction
The urinary bladder often responds to BOO with hypertrophy, accompanied by an augmentation of connective tissue components and replacement of proteins of the contractile apparatus of the smooth muscle cell, with their non-muscle (embryonic) isoforms, such as non-muscle myosin heavy chain, α-isoform of tropomyosin, calponin, β- and γ-actin.13

High bladder pressure induces adaptive changes in the bladder structure, which, in the long term, are visible as muscle enlargement and collagen deposition.14 The increase in connective tissue between muscle fibres and muscle bundles significantly decreases bladder elasticity and therefore bladder compliance.15 Obstruction-induced smooth muscle remodelling and hypertrophy are compensatory responses aimed to produce the increased force required to expel urine against the obstruction. These compensatory changes are associated with altered expression of contractile proteins and various signalling and regulatory proteins such as calmodulin, Rho-activated kinase and caveolins.16-18 Rho-kinase constitutes a main pathway, which regulates detrusor Ca²⁺ sensitisation, which is necessary for the detrusor muscle to maintain contraction.19

Bladder outlet obstruction and the ensuing muscle hypertrophy and collagen deposition within the bladder wall results in a significant decrease in detrusor blood flow and hence impaired oxygen diffusion to the tissues;20 furthermore an increased expression of Hypoxia Inducible Factor-a (HIF-a) is observed (Fig. A).21 During obstruction, the detrusor reduces its own oxygen supply by producing pressures that compress the small blood vessels.22,23 As a result to hypoxia, obstructed bladders appear hypervascular and partially denervated and exhibit alterations in the mitochondrial structure and function.24 and the glycogen content.25 Obstruction also induces protein oxidation in the detrusor smooth muscle26 and lactic acid due to the anaerobic metabolism accumulates causing contractile dysfunction.27 These findings suggest that ischemia and hypoxia may be responsible for the development of bladder dysfunction in BOO.28,29 It is not known whether this is mediated directly through an effect on the detrusor smooth muscle30 or as a result of neuronal loss and subsequent smooth muscle changes.31

Mitochondria-ATP-Glucose metabolism
Mitochondrial enzyme activity is crucial in the energy production and contractility of detrusor muscle and it has been shown to increase with the severity of partial bladder outlet obstruction in the mammal.32 As the obstruction progresses, increased oxidative stress in the detrusor muscle occurs, leading to a significantly higher incidence and proportion of mitochondrial DNA deletions.33

Electron microscopy evaluation of the obstructed rabbit bladder showed that mitochondria within detrusor muscle cells become progressively more swollen. Six weeks post-obstruction, similarly swollen mitochondria are also present in other cell types within the bladder wall, such as fibroblasts, Schwann cells, endothelium and perivascular smooth muscle. These findings of mitochondrial damage have been interpreted as evidence of ischemic...
damage of the bladder wall as a consequence of outflow obstruction. Similar mitochondrial damage has been noted in human detrusor smooth muscle cells in biopsy samples removed from patients with bladder outflow obstruction.

Currently, many investigators consider mitochondrial alteration as a crucial factor in voiding dysfunction and hypothesise that severe and irreversible mitochondrial damage, marked by disruption of outer membrane, could explain the frequent persistence of symptoms after removal of bladder outlet obstruction in men.

Furthermore, during obstruction, mitochondrial enzyme activity subsides thus leading to impaired oxidative metabolism, as evidenced by specific decreases in the activity of citrate synthase (CS), malate dehydrogenase and cytochrome oxidase. ATP provides most of the cellular energy required for maintenance of cell function. Adequate cytosolic ATP concentration is maintained by anaerobic metabolism of glucose to pyruvate and subsequent oxidative metabolism of pyruvate to CO₂ and H₂O within the mitochondria through the tricarboxylic acid (TCA) cycle and respiratory chain pathway. CS is the rate-limiting enzyme of the TCA cycle, which provides substrates for the respiratory chain. A reduction in respiratory chain substrates would lead to decreased oxidative phosphorylation (i.e., decreased ATP synthesis). Bladder biopsies from men with significant obstructive symptoms, secondary to BPH, have demonstrated a marked decrease in CS activity compared to bladder samples isolated from unobstructed men of the same age.

There is also evidence of reduced aerobic and increased anaerobic metabolism in obstructed bladders. Partial bladder outlet obstruction of the rabbit induces a shift from aerobic to anaerobic metabolism, as evidenced by the shift in glucose metabolism from CO₂ to lactic acid generation. Similarly, there is a marked decrease in the metabolism of pyruvate to CO₂.

Glycogen content
During obstruction, the bladder muscle reduces its own oxygen supply by producing pressures that compress the small blood vessels. This prompts parts of the muscle to function anaerobically and glycogen may be used as an alternative energy supplier. Upon chronic ischemic periods the bladder may adapt by increasing the amount of glycogen stored in muscles cells. In an animal model, Bas W.D. de Jong et al showed that glycogen deposition in the bladder wall is directly related to bladder function during obstruction; the strongest glycogen deposition was found in bladders having experienced the highest pressures, lowest compliance and highest contractility. At first, little deposition occurred close to the serosal side of the detrusor layer and later on, strongest accumulation appeared throughout the whole de-trusor layer up to the urothelium. The authors concluded that glycogen content is a clear marker of the severity of the functional changes that urinary bladder has undergone during obstruction and claimed that analyzing glycogen deposits may give insight in the severity of bladder damage and therefore contribute in making an accurate prognosis of bladder function.

Maintenance of normal detrusor function relies on sufficient oxygen and energy supplies and there is probably a crucial level below which hypoxia-induced muscle dysfunction ensues. In the compensated bladder, relief of the ischemia should result in an immediate restore of contractility. However, at some stage, ischemia-induced changes might become less reversible and the potential of the bladder to regenerate its function might be reduced.

Denervation
Several human bladder studies showed that there is a significant loss of innervation (denervation) associated with obstructive dysfunction secondary
to BPH\(^{34}\). Neurones are known to be very sensitive to hypoxic damage, with grey matter more easily damaged than white\(^{35}\). Denervation may arise because of damage to postganglionic parasympathetic neurones within the bladder wall and this damage may be caused by the transient bladder ischemia that occurs during obstructed micturition\(^{44}\). Moreover, partial bladder denervation during BOO is more prominent on the cholinergic than on the sympathetic side of the system, as the former is dominant in the bladder\(^{35}\). Cumming et al, reported a 56% reduction in the number of acetylcholine-positive nerves in bladder biopsies obtained from obstructed compared to nonobstructed men\(^{36}\). Counts of nerve profiles confirmed reduced density of autonomic innervation and not merely decreased concentration of AchE.

**Conclusion**

Bladder dysfunction secondary to BPH is a major affliction of aging men. Bladder modifies its structure in order to compensate the increased resistance to flow. As a result there is a significant decrease in detrusor blood flow, especially in the late period of the obstruction.

During the obstruction and hypoxia period, six major alterations of bladder wall morphology and detrusor biochemistry may be recognised (Fig. B):

1) Muscle enlargement and collagen deposition, 2) mitochondrial DNA deletions, mitochondrial damage and reduced mitochondrial substrate (e.g. glucose) utilisation, 3) decreased mitochondrial enzyme activity which leads to decreased oxidative metabolism and ATP synthesis, 4) reduced aerobic and increased anaerobic metabolism which leads to lactic acid accumulation, 5) glycogen deposition, as an alternative energy supplier and 6) reduced cholinergic nerve density and denervation.

In the case of long-lasting BOO, mitochondrial damage may become irreversible and this could explain the persistence of symptoms after relief of BOO in the male. Detrusor glycogen content could be probably used as a marker of the severity of alterations that have occurred within the bladder wall during obstruction. However, more studies in the human urinary bladder are required in order to confirm that hypothesis.

**Fig. A.** Pathophysiology of BPH and obstruction-induced alterations within the urinary bladder. BPH – benign prostate hyperplasia; BOO – bladder outlet obstruction; HIF-α – hypoxia induced factor α.
Περίληψη

Παθοφυσιολογικές μεταβολές στην ουροδόχο κύστη από την υποκυστική απόφραξη που προκαλεί η Καλοήθης Υπερπλασία του Προστάτη (ΚΥΠ).

Ανασκόπηση της βιβλιογραφίας

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Σκοπός: Η Καλοήθης Υπερπλασία του Προστάτη (ΚΥП) αποτελεί συνήθη αιτία υποκυστικής απόφραξης και πρόκλησης συμπτωμάτων από το κατάτερο ουροτοιχικό σύστημα (LUTS). Στο τοίχωμα της ουροδόχου κύστης συμβαίνουν σημαντικές λειτουργικές, βιοχημικές και μορφολογικές μεταβολές κατά την εξέλιξη της ΚΥΠ, ώστε να διατηρηθεί η ψυχιατρική λειτουργικότητά της. Μελέτες έχουν καταδείξει μειωμένη αιμάτωση του εξωστήρα μόνο όταν υπάρχει υποκυστική απόφραξη. Η παρούσα ανασκόπηση παρουσιάζει την απάντηση της ουροδόχου κύστης κατά την υποκυστική απόφραξη και επιδεικνύει στις μεταβολές και βιοχημικές προσαρμογές του κυστικού τοιχώματος παρουσία της υποξίας.

Μέθοδος: Πραγματοποιήθηκε ανασκόπηση της δημοσιευμένης βιβλιογραφίας, η οποία συμπεριέλαβε in vivo και in vitro μελέτες σε ανθρώπινους και ζωικούς ιστούς.

Αποτελέσματα: Κατά τη διάρκεια της απόφραξης και της υποξίας επεξεργάζεται μική υπερτροφία, εναπόθεση κολλαγόνου, βλάβη στα μυοχόνδρια, διαγραφής μυοχονδριακού DNA και μείωση της μυοχονδριακής ενζυμικής δραστηριότητας, με αποτέλεσμα τον μειωμένο οξειδωτικό μεταβολισμό και την ελαττωμένη σύνθεση ATP. Επίσης, παρατηρείται απρόβλεψη τον αναερόβιο μεταβολισμό και πιθανόν εναπόθεση γλυκογόνου, προκειμένου να ανευρεθούν εναλλακτικές πηγές ενέργειας από τα μικτά κύτταρα. Αποτέλεσμα αυτών των διαδικασιών είναι η συσσώρευση γαλακτικού οξέος στις λείες μικτές ίνες λόγω του αναεροβίου μεταβολισμού, η οποία προκαλεί συστολική δυσλειτουργία του εξωστήρα. Επιπρόσθετα, η υποξία προαγειά την απονέαρωση του τοιχώματος της κύστης και τη μείωση της πυκνότητας των χολενεργικών νευρώνων.

Συμπέρασμα: Η υποκυστική απόφραξη σχετίζεται με ποικίλες μορφολογικές και βιοχημικές μεταβολές στο τοίχωμα της κύστης που επηρεάζουν τη συσταλικότητα της. Η μακροχρόνια απόφραξη μπορεί να οδηγήσει σε μη αναστρέψιμες βλάβες στον εξωστήρα μου, με παραμονή της συμπτωματολογίας άκομα και μετά την άρση του κωλύματος.

Λέξεις Κλειδιά: Καλοήθης Υπερπλασία Προστάτη, Υποκυστική Απόφραξη, Ιασχίμα Εξωστήρα, Συμπτωματα Κατώτερου Ουροτοιχικού.
References


36. Siflinger-Birnboim A, Levin RM, Hass MA. Partial outlet obstruction of the rabbit urinary


45. Campbell JD, Agubosim S, Paul RJ. Compartmentation of metabolism and function in vas-


