Review

Mechanisms of Lower Urinary Tract Symptoms in Pelvic Ischemia

Kazem M. Azadzoi, Mike B. Siroky

Abstract: The etiology of lower urinary tract symptoms is poorly understood. The pathophysiology of detrusor instability, voiding dysfunction and pelvic pain in patients with non-obstructed bladder remains highly controversial. In the male, most cases of lower urinary tract symptoms are attributed to bladder outlet obstruction due to benign prostatic hyperplasia. However, urodynamic data have revealed that in approximately one third to more than one half of cases, lower urinary tract symptoms are not associated with enlarged prostate or bladder outlet obstruction. Interestingly, lower urinary tract symptoms questionnaires in women yield scores that are similar to their age-matched male counterparts. These observations imply that aging-associated sex-independent changes in bladder vasculature, nerves, smooth muscle and epithelium may play a role in the development of lower urinary tract symptoms. Epidemiologic studies have shown a close correlation between vascular occlusive disorders and the prevalence of lower urinary tract symptoms. International prostate symptom scores were found to be significantly worse in men with cardiovascular disorders than symptomatic patients without cardiovascular problems. Clinical trials have revealed a close correlation between decreased pelvic blood flow and severity of lower urinary tract symptoms in the elderly patients. Studies with experimental models of pelvic ischemia have shown that accumulation of reactive oxygen species in the ischemic bladder initiates a cascade of cellular, subcellular and molecular reactions. These reactions to ischemia appear to compromise bladder structure and function leading to neurodegeneration, smooth muscle instability, increased contractile activity, fibrosis and non-compliance. These observations collectively introduce a new concept in the pathophysiology of voiding dysfunction suggesting that pelvic ischemia may be an independent factor in the development of non-obstructed non-neurogenic overactive bladder and lower urinary tract symptoms.

Keywords: ischemia, oxidative stress, overactive bladder, LUTS

1. Introduction

The prevalence of lower urinary tract symptoms (LUTS) increases with aging in both men and women [1-4]. In men, lower urinary tract symptoms have traditionally been ascribed to bladder outlet obstruction due to benign prostatic hyperplasia (BPH). However, it is now recognized that all cases of LUTS are not necessarily due to prostatic enlargement or bladder outlet obstruction (BOO), suggesting other causes [5-8]. Several studies have documented that in approximately 34% of cases, prostate size is normal and LUTS are not associated with BOO [9, 10]. The incidence of non-obstructed overactive bladder and the development of LUTS without BOO appear to be much more common in the elderly population. It has been shown that in 80 years or older patients, approximately 60% of cases of LUTS are not associated with BOO [11]. Furthermore, surgical removal of the prostate fails to improve LUTS in approximately 25% of cases when patients are selected on the basis of symptoms [1, 12].

LUTS impact daily activities and the quality of life of elderly women with the same frequency as in elderly men. Interestingly, symptom questionnaires designed to document LUTS in women yields similar scores when compared with their age-matched male counterparts [6,7]. These studies have also shown that women provide scores on validated symptom indices that are identical to their male counterparts [7-9]. Urodynamic assessments have revealed that women suffer from age-associated bladder dysfunction in a similar manner as in men [2, 13]. These findings cumulatively suggest that BOO

*VA Boston Healthcare System and Boston University School of Medicine
*Corresponding author at: Building 1A, Room 315 (151)
VA Boston Healthcare System, 150 South Huntington Avenue
Boston, MA 02130, USA
Tel: +1 857-364-5602, Fax: +1 857-364-4540
Email: kazadzoi@bu.edu
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because of BPH do not adequately account for the pathophysiology of aging-associated LUTS. Based on these observations, it is likely that LUTS in the aging population with non-obstructed bladder involve multiple possible etiologies, including primary detrusor instability, impaired bladder smooth muscle contractility or a combination of the two.

The concept of non-obstructed detrusor overactivity is supported by urodynamic assessments followed by histological examination showing that aging results in specific functional and structural alterations in the bladder wall independent of obstruction and gender [14, 15]. Histomorphometric image analysis of human bladder samples have shown a significant decrease in smooth muscle/connective tissue ratio with aging in both genders independent of BOO [14, 15]. Transmission electron microscopy of bladder samples from patients ranging from 23 to 92 years of age has shown age-dependent increase in collagen accumulation in conjunction with atherosclerotic occlusive disease of small vessels, suggesting that aging may compromise microvasculature structure and hemodynamic characteristics of the urinary bladder [16].

One possible mechanism of LUTS that has received little attention is the role of pelvic arterial atherosclerosis and bladder exposure to ischemia and oxidative stress conditions. The incidence of vascular occlusive disease increases with aging, leading some to speculate that pelvic atherosclerosis and lower urinary tract ischemia may play a role in the development of overactive bladder and LUTS. Vascular risk factors and tissue exposure to ischemia and hypoxia have been frequently associated with significant changes in smooth muscle structure and function in various organs including penis [17], vascular smooth muscle [18], stomach and intestine [19], and lung [20]. Growing evidence from clinical studies and basic research suggest that ischemia interferes with lower urinary tract function and may be an independent factor in the development of non-obstructed non-neurogenic bladder overactivity and LUTS.

2. Clinical challenges of LUTS

Dysfunction of the lower urinary tract imposes important clinical challenges with significant impact on the quality of life. Severe cases of lower urinary tract dysfunction may result in infection, sepsis, renal failure and even death. Most common symptoms with less dramatic presentations include urinary frequency, urgency, nocturia, incontinence and enuresis. The prevalence of LUTS in institutionalized elderly patients is over 50% and represents one of the most common reasons for institutionalization [1, 5, 6]. The development of LUTS in the aging male may be influenced to some degree by BPH and the severity of BOO. However, clinical studies have revealed that most cases of BOO and LUTS in the elderly population do not correlate with BPH, suggesting mechanisms other than prostate enlargement [1, 5]. It is well recognized that α-blockers and therapeutic strategies for achieving androgen suppression reduces LUTS in men with BPH [21], possibly by diminishing prostate smooth muscle tension [22] and epithelial volume, respectively [23]. These clinical observations suggest both dynamic and static mechanisms of BOO. However, all cases of LUTS do not benefit from α-blockers and the specific dynamic forces contributing to BOO and LUTS are yet to be characterized. The mechanism of increased prostate tension with aging remains essentially unknown. The mechanism of LUTS improvement by α-blockers remains controversial. These unrecognized factors in the pathophysiology of LUTS impose major clinical challenges.

A poor correlation between the histological prevalence of prostatic hyperplasia, prostate volume, and the clinical syndrome of LUTS has been found in many studies [24-27]. The specific features of the hyperplastic prostate predisposing to the development of BOO remain essentially unknown [11, 22]. It is also reported that 47% of asymptomatic men had pressure-flow studies indicative of obstruction [28]. A discrepancy between LUTS and documented outflow obstruction has also been demonstrated by standardized symptom scores, which were introduced as an index of obstruction but have not been found to be specific for BPH [24-26]. These findings explain why treatments aimed at relieving BOO in elderly males fail to completely improve LUTS. For example, 25% of men undergoing transurethral resection of the prostate (TURP) will not have a favorable symptomatic outcome when patients are selected on the basis of symptoms [28]. A study of the correlation between LUTS, prostatic enlargement and BOO showed that only 3.4% of the variability in the American Urological Association (AUA) symptom score is attributable to prostate volume, 5.7% of the variability in peak flow rate is attributable to prostate volume, and 12.3% of the variability in the peak flow rate is attributable to AUA symptom score [29]. This data challenges the traditional theory of prostatic enlargement as the sole cause of BOO that leads to LUTS. These observations suggest that LUTS in the elderly involves, in addition to BPH, specific aging-related changes in the pelvis and lower urinary tract including the prostate and bladder. Cumulating evidence from clinical trials and basic research suggest that aging-associated pelvic atherosclerosis and lower urinary tract ischemia may play an important role in the development of LUTS in the elderly.

3. Clinical evidence of LUTS in pelvic ischemia

A close correlation between pelvic ischemia and bladder overactivity has been documented in the elderly men and women [30-39]. Pelvic blood flow recording with transrectal color Doppler ultrasonography has revealed significant bladder ischemia in the symptomatic elderly patients in comparison with asymptomatic younger controls [30-39]. Decreased bladder blood flow has significantly correlated with the severity of LUTS in these patients [30-39]. Other clinical studies have shown that LUTS improvement with alpha adrenocceptor blockers is associated with a significant increase in bladder blood flow [32, 37]. Marked human bladder ischemia after overdistention and a significant correlation between decreased blood flow and bladder non-compliance have also been documented [34, 36]. These findings are consistent with increased incidence of arterial occlusive disease and ischemic disorders with aging.
Epidemiologic studies have shown that a history of cardiovascular disease closely correlates with a higher risk of urinary incontinence [1, 8]. The close association between LUTS and erectile dysfunction may suggest pelvic arterial atherosclerosis as a unifying mechanism [40-42]. These studies have revealed a two-fold increase in the incidence of erectile dysfunction in men with voiding dysfunction in comparison with men who did not report any LUTS. The specific features of aging pelvis contributing to lower urinary tract dysfunction remain virtually unknown. Recent urodynamic data suggest that aging-associated alterations of pelvic vasculature and impairment of pelvic blood flow may play a role. It is thought that pelvic vascular insufficiency may be an independent factor in the development of non-obstructed non-neurogenic bladder overactivity and LUTS in the elderly population. The close association between erectile dysfunction and urinary incontinence correlates with progressive development of vascular occlusive disease in the elderly population [40-42]. Vascular risk factors such as smoking and hypertension has been reported to be associated with LUTS in men. The epidemiological correlation between erectile dysfunction, LUTS and vascular disease is interesting and may suggest an etiologic relationship.

Aging-associated pelvic atherosclerosis and prostate ischemia is thought to play a role in the dynamic mechanism of BOO that could result in LUTS without BPH. It is believed that ischemic prostate smooth muscle generates dynamic forces that could contribute to LUTS in the elderly male [31, 32]. The mechanism of increased smooth muscle tension in prostate ischemia may involve molecular reactions and differential changes in prostate nerves, receptors and smooth muscle cell contractile apparatus [31, 32]. Prostate blood flow is reduced in patients with documented vascular occlusive disease [31]. It has been shown that the status of prostate perfusion correlates with validated measures of LUTS [31]. Transrectal color Doppler ultrasonography of elderly patients with LUTS has shown a significant decrease in prostate blood flow in comparison with asymptomatic group of younger controls [30, 32]. It is also reported that improvement of LUTS with α-blockers is associated with significant increases in both prostate and bladder blood flow [32]. A close correlation between international prostate symptom score (IPSS) and vascular occlusive disease has been reported in the elderly men [43]. This study has revealed significantly worse IPSS scores in men with peripheral arterial occlusive disease than controls. Perfusion of the transition zone was found to be significantly lower, the resistive index was significantly higher, and the prostate glands were larger in patients with peripheral arterial occlusive disease [43]. These observations collectively suggest that aging-associated LUTS in the elderly are not entirely related to BPH and BOO or specific to the male gender. It is likely that LUTS in the elderly have a multifactorial etiology involving aging-associated changes in lower urinary tract blood vessels, nerves and smooth muscle cells.

4. Basic research evidence

4.1. Experimental models of pelvic ischemia

Finkenbeiner and Lapides were among the earliest to report that filling and distention reduce bladder wall blood flow [44]. These findings led them to postulate that bladder distention and subsequent exposure to ischemia may lead to bladder infection. This concept led to the introduction of clean-intermittent catheterization [45]. Studies with an experimental model have revealed considerable regional variation in bladder wall blood flow and oxygenation [46]. It was found that bladder perfusion and oxygen tension are greater at the bladder base in comparison with the dome. Obstruction of the bladder neck resulted in ischemia that appeared to be more pronounced at the bladder base [46]. Filling and distending the bladder led to a significant decrease in bladder wall perfusion and oxygenation. Spontaneous contractions of the bladder caused significant decreases in bladder wall blood flow in both obstructed and non-obstructed bladders [46]. In the obstructed bladder, the drop in bladder perfusion was more dramatic reaching to a mean of 58% of the level prior to contraction.

Other experimental models of pelvic and bladder ischemia includes vesical artery ligation and pelvic arterial atherosclerosis. Bilateral ligation of the vesical arteries was shown to induce extreme ischemia and hypoxia leading to bladder necrosis which resembled gangrene rather than sustained moderate ischemia [47, 48]. Unilateral ligation of the vesical artery produced mild to moderate ischemia and led to bladder non-compliance and hyperactivity with impaired smooth muscle contractile reactivity to both adenosine and electrical field stimulation within two weeks after ligation. At week 4 after unilateral arterial ligation, however, these changes returned to normal levels showing in vivo and vitro characteristics similar to the sham-operated group [47, 48]. It is thought that regeneration of collateral circulation at week 4 after unilateral ligation of the vesical artery restores bladder blood flow to the normal levels.

Because of lack of a feasible experimental model and lack of equipment to document pelvic and bladder blood perfusion, little was known about regulation of bladder hemodynamics until laser Doppler flowmeter enabled real-time monitoring of bladder blood flow changes in the empty and distended bladder [49-51]. Laser Doppler flowmeter technology revealed that bladder blood flow significantly decreases with high-pressure filling. Contraction against an obstructed outlet was found to induce regional bladder ischemia and hypoxia [49-52]. Subsequent studies with laser Doppler flowmeter explored some of the regulatory pathways of bladder microcirculation resistance showing multiple neuropharmacologic and biomechanical mechanisms [53]. These studies showed that bladder microcirculation resistance and blood flow may be primarily regulated by nitric oxide and mechanical changes in the shape of the bladder and its vasculature [53]. It appears that neural mechanisms and mechanical changes with bladder filling, contraction and emptying favor blood flow to the bladder base than the dome [53]. It was latter shown that outlet obstruction and unilateral ischemia lead to similar genetic and cellular changes in the bladder [54]. It was reported that increasing bladder pressure with filling produces significantly
greater ischemia and hypoxia in the obstructed bladders than controls [54]. Intermittent hypoxia in the obstructed bladder was shown to generate a significant amount of hypoxyprobe-1–protein adducts [55, 56]. Regional ischemia in the partially obstructed bladder was found to be associated with selective metabolic dysfunction of the smooth muscle cells characterized by decreases in mitochondrial function, and sarco/endoplasmic reticulum calcium ATPase activity [55]. Metabolic and cellular changes appeared to closely correlate with upregulation of hypoxia inducible factor-1 alpha and an inflammatory response in the initial stages of bladder outlet obstruction [56]. This response in the obstructed bladder is thought to be initiated by intermittent hypoxia and appears to be followed by smooth muscle hypertrophy and fibrosis [57].

4.2. Bladder reactions to pelvic ischemia

Basic research with experimental models of pelvic arterial atherosclerosis suggests that chronic ischemia alters bladder structure and function and leads to a cascade of cellular, subcellular, and molecular reactions.

4.2.1. Functional changes in bladder contractile properties

Studies with the experimental model of arterial atherosclerosis have shown that pelvic ischemia produces significant changes in bladder contractile properties [59-65]. In this model, the pattern of contractile changes correlates with the degrees of bladder ischemia. Moderate ischemia produces bladder overactivity manifested as a significant increase in the frequency of spontaneous bladder contractions [61]. Bladder overactivity under the moderate ischemia conditions was associated with increased amplitude of spontaneous contractility of bladder smooth muscle cells and increased contractile responses to muscarinic receptor agonists and electrical field stimulation [61]. Cystometric examination of this model has revealed that while moderate bladder ischemia causes detrusor overactivity, severe bladder ischemia produces an adverse effect on bladder contractions. Contrary to moderate ischemia, severe ischemia appears to reduce the amplitude of intravesical pressure during contraction in-vivo and diminish the reactivity of bladder smooth muscle to muscarinic receptor agonists and electrical field stimulation [61]. Cystometric data have shown that severely ischemic bladders also tend to contract more frequently but the force of contraction is severely reduced in comparison with moderately ischemic bladders. Mild ischemia with less than 40% decrease in bladder blood flow had no significant effect on the frequency of bladder contractions.

The mechanism of bladder overactivity in moderate ischemia appears to involve oxidative stress, free radical incursion of smooth muscle cells and nerve fibers, and accumulation of cyclooxygenase and lipoxygenase products [59, 60]. Western blotting analysis of moderately ischemic bladder tissues have shown marked changes in 5-lipoxygenase, cyclooxygenase-1 and cyclooxygenase-2 protein expression and disproportionate alterations of leukotrienes and prostaglandins production [59, 60]. Alterations of lipoxygenase and cyclooxygenase expression in the moderately ischemic bladder closely correlate with bladder smooth muscle dysfunction. The data suggest that increased levels of leukotrienes dominate bladder tone and may play an important role in increased smooth muscle contractions and detrusor instability under the ischemic conditions. Subsequent studies have demonstrated that alterations of the cyclooxygenase and lipoxygenase pathways are associated with accumulation of noxious elements that appear to result from oxidative and nitrosative activities within the ischemic bladder layers [60]. It was found that recurring hemodynamic disturbances and rapidly fluctuating perfusion and oxygenation of the frequently contracting ischemic bladder generate free radicals. It is thought that, under the ischemic conditions, antioxidant deficiency and malfunctioning antioxidant enzymatic system allow free radical production to continue unchecked [60]. The marker of oxidative stress isoprostane 8-epi PGF2α has been detected in the early and late stages of bladder ischemia. Oxidatively modified products and eicosanoids are known to interfere with bladder smooth muscle contractions, suggesting that free radicals generated by overactivity may contribute to further bladder instability [59, 62]. Another possible mechanism of bladder overactivity in ischemia may relate to activation of afferent signaling via tachykinin containing nerves and neurokinin receptors. Ischemia appears to upregulate neurokinin-2 receptor gene expression, stimulate sensory nerve fiber outgrowth, and increase epithelial tachykinin production [63]. Under the ischemic conditions, the bladder neurokinin-2 receptor seems to become more reactive than Neurokinin-1 and Neurokinin-3 receptors [63]. Increased tachykinin containing nerves in bladder ischemia may imply afferent signaling and activation of tachykinin production by silent sensory fibers.

4.2.2. Structural changes in bladder smooth muscle and nerve fibers

An important mechanical change in the ischemic bladder wall is non-compliance [58]. The mechanism of ischemia-associated non-compliance appears to involve changes in the smooth muscle and connective tissue...
composition and alterations of the fibroelastic properties of the bladder wall. Fibrosis appears to be the most prominent histopathologic feature of ischemic non-compliant bladder [58]. Histologic and histomorphometric analysis of ischemic non-compliant bladder have revealed marked deposition of collagen, loss of smooth muscle, structural changes in the urothelium, thickening of the lamina propria and diffuse dense fibrosis of the submucosal layer, as shown in Figure 1 [58]. The extent of structural damage in bladder layers was shown to closely correlate with the severity of bladder ischemia [58]. Transmission electron microscopy of ischemic bladder tissues have shown structural changes in mitochondria with distinct characteristics typical of oxidative damage characterized by decreased mitochondrial granules, complete loss of granules, and mitochondrial membrane thickening, as shown in Figure 2 [64]. These mitochondrial structural changes appeared to be more evident within the muscular layer of the ischemic bladder [64]. In addition, disrupted smooth muscle fibers with separated and twisted muscle cells, nuclear deformation, and sporadic vacuolization have been documented in the ischemic bladder tissues [64]. Smooth muscle cell damage and collagen deposition closely correlate with loss of neural structural integrity and neurodegeneration in the ischemic bladder [60, 64]. Immunohistochemical studies have shown a significant decrease in the number of nerve fibers per high power field in the ischemic bladder tissues in comparison with age-matched controls [60, 64]. Surviving nerve fibers in the ischemic bladder were found to be hypertrophic [60].

It is believed that, under the ischemic conditions, the bladder undergo a number of adaptations to increase metabolic capacity to provide energy for detrusor overactivity. These adaptations impose an enormous burden on bladder mitochondria, the key players in energy production. In the initial stages of overactivity, the mitochondrial respiratory apparatus appears to cope with high energy demand [66]. In long-term overactivity, however, excessive energy demand exhausts the mitochondrial energy transduction system and initiates structural demolition and loss of granules [66]. This destructive process within the mitochondrial respiratory apparatus is thought to be mediated by oxidative stress and malfunctioning of mitochondrial complexes I to V of energy production [66]. Free radical incursion of mitochondria and subsequent deterioration of mitochondrial respiratory apparatus is believed to contribute to smooth muscle cell and nerve fiber dysfunction, structural damage, and degenerative changes of the bladder wall. Nerve damage in the ischemic bladder could result from free radical activity within neural structures or after nerve fibers exposure to toxic oxidative products originating from surrounding tissues. Another degenerative mechanism in ischemia may relate to oxidative incursion of endoplasmic reticulum (ER), an

Fig. 1. Structural changes of urothelium in bladder ischemia detected by Masson's trichrome staining (x 100 magnification). Marked thickening and disruption of the mucosa along with vacuolization, dense fibrosis the sub-urothelial layer, and smooth muscle atrophy are evident in the ischemic bladder. (From Azadzoi et al, J Urol 169:1885, 2003).
important regulator of protein processing and folding [67]. When oxidized, ER accumulates misfolded proteins leading to pathologic malfunctioning protein aggregates. Accumulation of misfolded and/or aggregated proteins is known to play a central role in degeneration of smooth muscle cells and nerve fibers [67].

4.2.3. Molecular reactions in bladder ischemia

Factors contributing to cellular and molecular reactions in bladder ischemia may include nutrient deficiency, hypoxia, lack of perfusion to remove metabolic waste and accumulation of free radicals and cytotoxic/neurotoxic elements [65]. In the healthy bladder, free radicals are tightly regulated by homeostatic mechanisms. Cellular antioxidant defense system neutralizes noxious radicals to protect tissues from oxidative injury. In bladder ischemia, lack of perfusion, nutrient deficiency and hypoxia impair the antioxidant defense system allowing free radicals to accumulate, initiating oxidative reactions and leading to toxic waste products [60, 64, 65]. Similar changes have been documented in experimental models of bladder outlet obstruction [55, 56]. Increasing bladder pressure with filling causes intermittent hypoxia in the obstructed bladder and produces hypoxprobe-1–protein adducts [55, 56]. Intermittent ischemia initiates a series of oxidative reactions mediated by superoxide (O$_2^-$) that rapidly interacts with nitric oxide (NO) to generate additional radicals via the nitrosative pathway [66]. Oxidative and nitrosative reactions in bladder ischemia activates downstream molecular pathways leading to deterioration of epithelium, smooth muscle cells, microvasculature, and nerve fibers by means of lipid peroxidation, protein oxidation and DNA damage [55, 56]. Oxidative reactions in the ischemic bladder are associated with upregulation of oxidative stress-sensitive enzymes superoxide dismutase (SOD) and aldose reductase (AR) [64]. SOD is an enzyme that catalyzes the dismutation of O$_2^-$ into oxygen and hydrogen peroxide and is known to defend cells and reduce the damage caused by peroxidation [67]. SOD is known to prevent free radical activity and reverse oxidative stress-associated cell injury [67]. Inhibition of SOD has been shown to increase oxidative injury and abolish the late phase of ischemic

**EPITHELIAL INJURY AND MITOCHONDRIAL REACTIONS**

**CONTROL**

**ISCHEMIC BLADDER**

*Fig. 2.* Subcellular structural changes in the ischemic bladder detected by transmission electron microscopy (reduced from 23,000x). This figure shows mucosal structural damage, swollen mitochondria, loss of mitochondrial granules, and mitochondrial membrane deformation in bladder ischemia. Black arrows point to the mucosal membrane. White arrows point to the mitochondria. (*From Azadzoi et al, J Urol 183:362, 2010*).
preconditioning [67]. AR is another oxidative stress-sensitive enzyme that reduces cytotoxic aldehydes and glutathione conjugates of aldehydes derived from lipid peroxidation [68]. AR was shown to protect smooth muscle cells from oxidative injury in blood vessels [68].

Studies of experimental models have shown that pelvic ischemia and bladder exposure to hypoxia and oxidative stress initiates a cascade of molecular reactions involving hypoxia inducible factor (HIF), transforming growth factor beta (TGF-beta), vascular endothelial growth factor (VEGF) and nerve growth factor (NGF). The data suggest a close correlation between molecular reactions and structural changes in bladder mucosa, smooth muscle cells, microvasculature and nerve fibers [65]. In the ischemic bladder, transcriptional molecular changes appear to be more distinctive in comparison with changes seen in the transitional level. Upregulation of HIF, TGF-beta and NGF gene expression were found in association with significant increases in their protein expression. However, increased levels of VEGF gene expression appeared to have no significant effect on VEGF protein levels [65]. It is believed that molecular reactions to ischemia initiate a cascade of downstream pathways involving ischemic cell survival signaling. Activation of cell survival signaling under the ischemic conditions impairs bladder smooth muscle contractility and leads to degeneration of bladder smooth muscle cells and nerve fibers.

Upregulation of HIF-1 alpha gene and protein expression in the ischemic bladder may suggest tissue response to low oxygen tension (Figure 3). Upregulation of HIF in bladder ischemia is associated with specific changes in mitochondrial membrane and granules seen in oxidative stress conditions [65]. Upregulation of TGF-beta gene and protein expression in bladder ischemia is accompanied by structural changes in smooth muscle cells, increased connective tissue, collagen invasion of nerve fibers and sporadic vacuolization of the ischemic bladder layers (Figure 3) [64, 65]. TGF-beta may play a central role in bladder fibrosis as it is implicated in the induction of collagen deposition and soft tissue fibrosis [69]. TGF-beta regulates the production of extracellular matrix and maintains the relative balance of smooth muscle and collagen in bladder wall [69]. It is thought that under the ischemic conditions, TGF-beta upregulates its own mRNA and increases its receptor expression [69]. TGF-beta regulates ischemia-associated collagen deposition and appears to play a

![HIF Expression](image1.png)

![TGF-beta Expression](image2.png)

**Fig. 3.** Molecular reactions in bladder ischemia. Real-time PCR and western blot analysis of ischemic bladder tissues have revealed a significant increase in HIF and TGF-beta gene and protein expression. The data is presented as mean ± standard error of the mean. * indicates significant change versus controls. *(From Azadzoi et al, J Urol 186:2115, 2011).*
central role in impairment of the fibroelastic properties of the detrusor tissue that result in bladder non-compliance [69]. These observations in the experimental models are consistent with clinical observation of a close correlation between decreased human bladder blood flow and non-compliance [35].

Upregulation of VEGF gene expression in bladder ischemia may be an intrinsic defensive reaction to stimulate angiogenesis to restore smooth muscle function and repair structural damage (Figure 4) [65]. Studies of experimental models have shown that upregulation of VEGF gene expression in bladder ischemia conditions do not increase VEGF protein levels [65]. One possibility may be that, under the hypoxic and oxidative stress conditions, smooth muscle and endothelial cells are not capable of synthesizing VEGF protein. The ischemic and hypoxic environment may not be feasible to VEGF protein synthesis. Another possibility is that excessive TGF-beta levels and the induction of collagen synthesis may result in containment of VEGF synthesis. Studies of vascular tissues have shown that ischemia and hypoxia stimulate angiogenesis via angiogenic growth factors and VEGF serves as a survival factor for endothelial cells [70]. Experimental inhibition of VEGF causes structural damage and detachment of endothelial cells from blood vessels [29].

Upregulation of HIF under the hypoxic conditions is shown to upregulate VEGF expression to stimulate neangiogenesis [70]. NGF upregulation in the ischemic bladder may also be an intrinsic defensive response to stimulate neural outgrowth and protect neural structural integrity against free radical incursion (Figure 4). This intrinsic reaction, however, seems ineffective as gene expression of p75 NGF receptor significantly decreases immediately after the induction of bladder ischemia [60]. Downregulation of NGF receptors under the ischemic conditions results in impairment of NGF action to stimulate new neural outgrowth and prevent neurodegeneration in the bladder [60]. These molecular reactions imply a well-coordinated intercommunication between HIF, VEGF and NGF that seems to fail to protect the bladder vasculature, nerves and smooth muscle cells against ischemic and oxidative stress injury. These observations collectively suggest the need for newer therapeutic strategies to target basic mitochondrial processes such as energy metabolism or free-radical generation to prevent or reverse bladder wall degeneration and neuropathy in the dysfunctional bladder.

**Fig. 4.** Molecular reactions in bladder ischemia. Real-time PCR analysis of ischemic bladder tissues has shown significant increases in both VEGF and NGF gene expression. Western blotting has shown that while NGF protein expression significantly increases, VEGF protein levels remain unchanged in the ischemic bladder. The data is presented as mean ± standard error of the mean. * indicates significant change versus controls. (From Azadzoi et al, J Urol 186:2115, 2011).
5. Summary

A new concept has been introduced in the pathophysiology of lower urinary tract symptoms, namely pelvic arterial insufficiency, as underlying the common clinical problem of non-obstructed non-neurogenic overactive bladder. Undoubtedly, enlarged prostate in some men is likely to induce bladder outlet obstruction and symptoms. However, recent clinical data suggest that this subset may be very small. It is now widely accepted that, in addition to prostatic enlargement, unrecognized factors in lower urinary tract contribute to lower urinary tract symptoms in the elderly men. The pelvic ischemia theory that challenges the traditional view of lower urinary tract symptoms is supported by several epidemiologic studies, clinical investigations, and basic research findings showing a close correlation between pelvic atherosclerosis, oxidative stress, and the development of lower urinary tract dysfunction. Vascular occlusive disorders in the elderly men are highly prevalent. Impairment of bladder and prostate blood flow closely correlates with the severity of lower urinary tract symptoms in the elderly patients. It is believed that ischemia triggers a cascade of signaling pathways that result in structural damage and malfunctioning of the bladder nerves, receptors, synaptic membranes and contractile components of the smooth muscle cells. These alterations collectively contribute to increased bladder smooth muscle contraction and may lead to detrusor instability and lower urinary tract symptoms. Further insight into the mechanistic pathways of bladder overactivity in pelvic ischemia may allow more accurate and systematic assessment of LUTS in patients without bladder outlet obstruction and provide comprehensive information on unexplored neural, receptor and cellular aspects of increased bladder smooth muscle tension.

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References


