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Thiago Souto Hemerly

Luisa Resende Tenório de Albuquerque

Ruan Pimenta

Vanessa Guimaraes Schreiter

See next page for additional authors

Authors

Carlos Henrique Suzuki Bellucci, Thiago Souto Hemerly, Luisa Resende Tenório de Albuquerque, Ruan Pimenta, Vanessa Guimaraes Schreiter, Sabrina Thalita dos Reis, Jose de Bessa Jr, Katia Ramos Moreira Leite, Alberto Antunes, Boopathi Ettickan, William C. Nahas, and Cristiano Mendes Gomes

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Downregulation of *PIEZO2* in the Detrusor of Men With Bladder Outlet Obstruction and Its Association With Urinary Retention and Decreased Bladder Compliance

Carlos Henrique Suzuki Bellucci[1], Thiago Souto Hemerly[1], Luisa Resende Tenório de Albuquerque[1], Ruan Pimenta[2], Vanessa Guimaraes Schreiter[2], Sabrina Thalita dos Reis[2], Jose de Bessa Jr[3], Katia Ramos Moreira Leite[2], Alberto Antunes[1], Ettickan Boopathi[4], William C. Nahas[1], Cristiano Mendes Gomes[1]

[1]Division of Urology, University of Sao Paulo School of Medicine, Sao Paulo, Brazil
[2]Laboratory of Medical Investigation (LIM55), University of Sao Paulo School of Medicine, Sao Paulo, Brazil
[3]Division of Urology, State University of Feira de Santana, Feira de Santana, Brazil
[4]Department of Medicine, Center for Translational Medicine, Thomas Jefferson University, Philadelphia, PA, USA

Purpose: Recent research has highlighted the mechanotransducer PIEZO2 as a crucial factor in lower urinary tract function, demonstrating associations with bladder compliance (BC), bladder wall thickening, and elevated bladder pressure. We explored the hypothesis that *PIEZO2* expression may be associated with lower urinary tract dysfunction in men with bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH).

Methods: The study included a consecutive series of patients undergoing open prostatectomy for BPH at our hospital between September 2014 and January 2016. All participants underwent comprehensive preoperative evaluations, including urodynamic assessments. During prostatectomy, a full-thickness fragment of the bladder wall was obtained for subsequent *PIEZO2* gene expression analysis. Cadaveric organ donors served as the control group.

Results: *PIEZO2* expression was downregulated in the detrusor muscle of men with BPH compared to the control group. Among patients with BPH, those experiencing urinary retention and requiring an indwelling catheter exhibited significantly lower *PIEZO2* messenger RNA (mRNA) expression than patients capable of spontaneous voiding. *PIEZO2* mRNA expression was similar in men with and without detrusor overactivity. Additionally, a positive correlation was found between *PIEZO2* mRNA expression levels and BC.

Conclusions: Our findings indicate that *PIEZO2* is downregulated in the detrusor muscle of men with BPH, particularly in those experiencing urinary retention and those with reduced BC. These results suggest a potential role for PIEZO2 in BOO-induced bladder dysfunction. Further research is required to clarify the role of PIEZO mechanotransducers in the bladder and to explore their therapeutic implications.

Keywords: PIEZO 2 channel; Urinary bladder neck obstruction; Humans; Lower urinary tract symptoms

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- **Research Ethics:** The experiments involving human bladder tissues received approval from the University of São Paulo School of Medicine Review Board (approval number: 3.083.924). The patients agreed to participate following full disclosure of the study's objectives, and written informed consent was obtained from each individual.
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

Corresponding author: Carlos Henrique Suzuki Bellucci
https://orcid.org/0000-0002-3570-859X
Division of Urology, University of Sao Paulo School of Medicine, Av. Dr. Arnaldo, 455 - Cerqueira César, Sao Paulo, Brazil
Email: carloshenriquesb@yahoo.com.br
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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common source of lower urinary tract symptoms (LUTS) and the primary cause of bladder outlet obstruction (BOO) in adult men [1, 2]. BOO can lead to deterioration of bladder function and changes in bladder morphology, with consequences including smooth muscle hypertrophy, bladder wall fibrosis, and eventual urinary retention [3-5]. Initially, smooth muscle cells undergo hypertrophy as an adaptive response to pathological stimuli. However, prolonged stimulation may cause the detrusor muscle to develop irreversible decompensation and contractile dysfunction [6, 7]. Therefore, elucidating the molecular mechanisms underlying pathological detrusor hypertrophy could benefit patients experiencing BOO and impaired detrusor contraction.

Mechanical features, including stretching, shear stress, bending, and compression, are essential for maintaining organ structure and function [7-10]. The importance of mechanical forces is well-recognized in the regulation of electrical coupling, metabolic reprogramming, extracellular matrix remodeling, and the structural properties of the bladder and other contractile organs [7-9, 11-13]. High mechanical stress is a primary factor contributing to bladder hypertrophy [10, 14-17]. Smooth muscle cells detect these diverse mechanical stimuli and translate them into biochemical signals, potentially leading to organ dysfunction [7, 14-16].

The mechanisms by which mechanical sensors coordinate the activity of detrusor smooth muscle cells and their mechanical environment remain elusive. Mechanically activated cation channels are a specialized type of mechanotransducer that respond rapidly to changes in mechanical force, either by exciting cell membranes or by triggering calcium signaling [9]. Recent discoveries have revealed that genes in the *PIEZO* family, specifically *PIEZO1* and *PIEZO2*, encode critical components of mammalian mechanically activated cation channels. These findings characterize a family of mammalian genes whose expression is both necessary and sufficient for the generation of mechanically activated cationic currents [18].

Both *PIEZO1* and *PIEZO2* are expressed in the bladder and urethra, predominantly in the urothelium but also in the interstitial cells of Cajal and smooth muscle cells [19-22]. The exact function of these proteins in the micturition cycle is not fully understood; however, their role as mechanosensitive ion channels, essential for low-threshold bladder stretch sensing and urethral micturition reflexes, is supported by various studies [19, 21-23].

A recent study identified PIEZO2 as an essential mediator of urinary tract function [22]. PIEZO2-deficient individuals were clinically examined, with many exhibiting LUTS, such as diminished bladder sensation, infrequent voiding, urge incontinence, and difficulty voiding. Animal experiments also demonstrated that mechanosensory stimuli activate PIEZO2 in urothelial cells, which in turn prompts bladder relaxation during the filling phase. Furthermore, PIEZO2 deficiency was linked to reduced bladder compliance (BC). The research also revealed that PIEZO2-deficient mice (Cre lines with Piezo2 gene knockout in control sacral level S1 dorsal root ganglion neurons) exhibited bladder wall thickening and experienced higher bladder pressure during voiding compared to their wild-type counterparts [22].

Considering recent findings implicating PIEZO2 as an essential mediator of lower urinary tract function that is associated with BC, bladder wall thickening, and increased bladder pressure, we explored the hypothesis that *PIEZO2* expression is associated with lower urinary tract dysfunction in men with BOO due to BPH.

MATERIALS AND METHODS

Patients

From September 2014 to January 2016, we enrolled a consecutive series of patients undergoing open prostatectomy for BPH at our hospital in the study. We excluded patients with a previous history of pelvic surgery or radiotherapy, urethral stricture, bladder stones, prostate or bladder cancer, or neurological diseases affecting lower urinary tract function, along with those who were unable to void during urodynamic investigation.

All patients underwent a comprehensive assessment that included medical history, International Prostate Symptom Score (IPSS), physical examination with digital rectal examination, prostate-specific antigen level testing, urine analysis and culture, and transabdominal sonography to evaluate the kidneys, bladder, prostate volume, and postvoid residual (PVR) urine volume. Additionally, all patients underwent urodynamic testing, which evaluated the following parameters: maximum cystometric capacity (MCC), BC, presence of detrusor overactivity (DO), maximum urinary flow rate (Qmax), detrusor pressure at maximum urinary flow (PdetQmax), and PVR urine volume. Detrusor contractility was assessed using the bladder contractility index (BCI). A BCI of less than 100 was considered

indicative of weak contractility, a BCI between 100 and 150 normal contractility, and a BCI greater than 150 strong contractility [24]. BOO was evaluated using the BOO Index (BOOI), with a BOOI greater than 40 signifying obstruction and a BOOI less than 20 indicating an unobstructed outlet [24]. These definitions align with the terminology established by the International Continence Society [25].

A full-thickness fragment of the bladder wall, measuring 1.0×0.5 cm, was obtained during prostatectomy. The mucosa and adventitia were removed, and the muscular layer was frozen in RNAlater solution at -20°C.

The control group consisted of 9 cadaveric organ donors (median age, 35.1±14.5 years), each with a smooth and macroscopically normal bladder wall. At the conclusion of organ-harvesting surgery, a bladder sample was collected using the same technique employed for the patients with BPH.

RNA Extraction and Quantitative Real-Time Polymerase Chain Reaction

Detrusor biopsies were prepared for gene expression analyses of *PIEZO2*. RNA extractions were performed using the mirVana kit (Ambion, Austin, TX, USA) in accordance with the manufacturer's instructions. The concentration of the extracted RNA was determined using an ND-1000 spectrophotometer (NanoDrop, Wilmington, DE, USA). The total RNA obtained was then used to synthesize complementary DNA (cDNA) using a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA). We diluted 50 ng/μL of RNA in 20 μL of nuclease-free water. cDNA synthesis was performed using the Veriti Thermal Cycler (Applied Biosystems) with the following parameters: 10 minutes at 25°C, 120 minutes at 37°C, and 5 minutes at 85°C. The cDNA was used immediately after synthesis. Expression levels of PIEZO2 (Primer Hs00401026_m1) were analyzed via quantitative real-time polymerase chain reaction (qPCR) using the ABI 7500 Fast Real-Time PCR System (Applied Biosystems). Beta-2 microglobulin (Primer Hs00187842_m1-B2m) served as an endogenous control due to its normal and homogeneous expression, facilitating the analysis of *PIEZO2* expression. Gene expression was evaluated by qPCR and quantified using the 2-ΔΔCT method [26].

Statistical Analysis

To compare the levels of *PIEZO2* messenger RNA (mRNA) expression in the BPH and control groups, the Mann-Whitney U-test was employed. The Student t-test was used to compare *PIEZO2* mRNA expression levels between patients with indwelling catheters and those with voiding dysfunction. Spearman coefficient correlation analysis was utilized to quantify the relationship between BC levels and *PIEZO2* expression levels. Data are presented as absolute values, frequencies, medians with interquartile ranges (IQRs), and means±standard deviations. The Shapiro-Wilk test was conducted to assess the normality of the data distribution. Statistical analysis was performed using GraphPad Prism 9.0 (GraphPad Software Inc., La Jolla, CA, USA), with P-values of 0.05 or less considered to indicate statistical significance.

RESULTS

The study included 19 men, with a median age of 70.0 years (IQR, 66.0–76.0 years). The indication for surgery was urinary retention in 12 patients (63.2%) and LUTS refractory to medical therapy in the remaining 7 (36.8%). All patients with urinary retention had failed at least 2 attempts at catheter removal, despite receiving alpha-blocker treatment for a minimum of 4 weeks. The median prostatic specific antigen level was 5.6 ng/mL (IQR, 2.9–12.1 ng/mL), and the median prostate volume

Table 1. Urodynamic parameters in men with BPH

Urodynamic parameter	Value
MCC (mL)	330.0 (200.0–380.0)
DO	12 (63.2)
BC (mL/cm H_2O)	20.0 (15.0–38.0)
Qmax (mL/sec)	5.0 (2.0–8.0)
PdetQmax (cm H_2O)	89.0 (52.0–110.0)
PVR (mL)	183.0 (80.0–235.0)
BOOI	72.0 (42.0–100.0)
>40	15 (78.9)
20–40	3 (15.9)
<20	1 (5.2)
BCI	107.0 (100.0–135.0)
<100	4 (21.0)
100–150	13 (68.5)
>150	2 (10.5)

Values are presented as median (interquartile range) or number (%).
BPH, benign prostatic hyperplasia; MCC, maximum cystometric capacity; DO, detrusor overactivity; BC, bladder compliance; Qmax, maximum urine flow; PdetQmax, detrusor pressure during maximum urine flow; PVR, postvoid residual; BOOI, bladder outlet obstruction index; BCI, bladder contractility index.

was 114.0 cm^3 (IQR, 98.0–180.0 cm^3). For patients not experiencing urinary retention, the median IPSS was 28.0 (IQR, 18.0–33.0). The urodynamic parameters are detailed in Table 1.

The expression profile of the *PIEZO2* gene in the detrusor of BPH specimens (0.0006 ± 0.0003) was found to be downregulated compared to that of the control group (0.0020 ± 0.0020, P = 0.01) (Fig. 1).

Among patients with BPH, those experiencing urinary retention with an indwelling catheter showed significantly lower *PIEZO2* mRNA expression levels than patients who could void spontaneously (0.0005 ± 0.0003 vs. 0.0008 ± 0.0002, respectively; P = 0.04) (Fig. 2A). No significant difference in *PIEZO2* mRNA expression was found between men with and without DO (0.0005 ± 0.0003 vs. 0.0008 ± 0.0004, respectively; P = 0.128) (Fig. 2B).

A positive correlation was observed between *PIEZO2* mRNA expression levels and BC (r = 0.53, P = 0.018) (Fig. 2C). The expression of *PIEZO2* mRNA was not influenced by factors including age, prostate volume, MCC, Qmax, PdetQmax, PVR urine volume, BOOI, or BCI (data not shown).

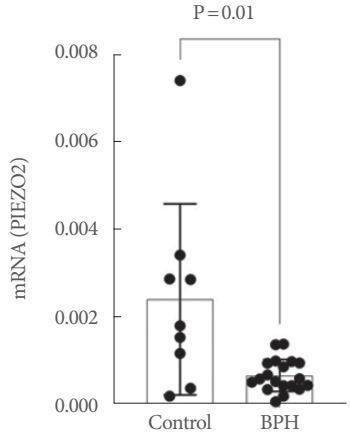

Fig. 1. PIEZO2 messenger RNA (mRNA) expression in men with benign prostatic hyperplasia (BPH) compared to controls.

DISCUSSION

PIEZO channels are crucial for transducing mechanical stimuli into biological responses, and they play key roles in a variety of physiological processes [27]. These structures fulfill diverse biological functions across human systems. Increasing evidence points to the involvement of PIEZO channels in the function of the lower urinary tract, yet their role in human pathologies is not fully understood. This study represented an exploratory investigation of the association between *PIEZO2* expression in the detrusor smooth muscle and lower urinary tract dysfunction in men with BOO due to BPH. We found that men with BOO resulting from BPH exhibit downregulation of *PIEZO2* expression. Furthermore, our results suggest a positive correlation between *PIEZO2* expression and BC.

Currently, limited evidence is available regarding the role of PIEZO-mediated mechanotransduction in bladder contraction and relaxation, particularly under pathological conditions. We opted to investigate *PIEZO2* expression in men with BPH following recent findings by Marshall et al. [22], which identified

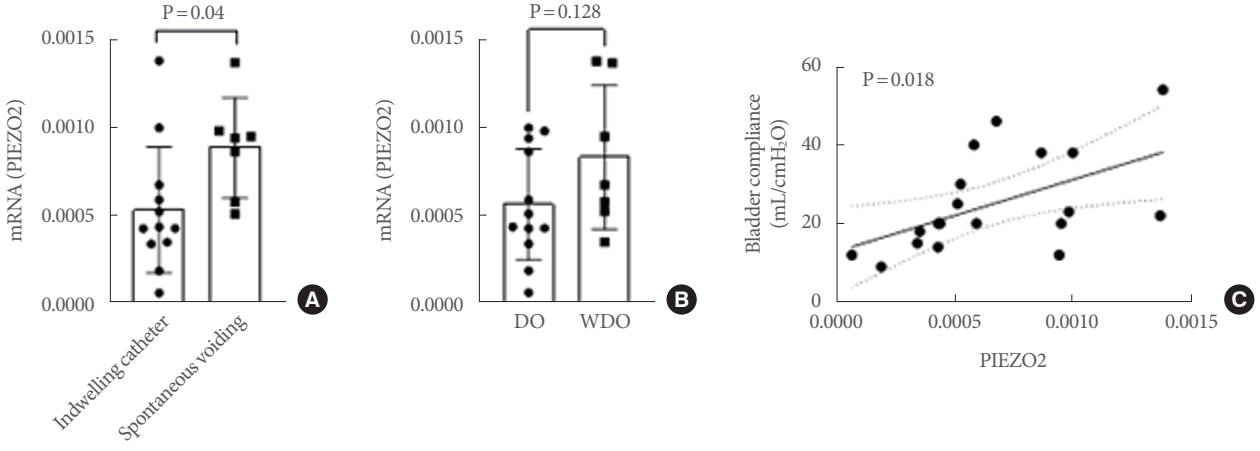

Fig. 2. (A) PIEZO2 messenger RNA (mRNA) expression in patients with urinary retention compared to patients with spontaneous voiding. (B) PIEZO2 mRNA expression in patients with DO versus those without DO. (C) Correlation between PIEZO2 mRNA expression and bladder compliance in 19 men with BPH. BPH, benign prostatic hyperplasia; DO, detrusor overactivity; WDO, without detrusor overactivity.

PIEZO2 as a key mechanotransducer in lower urinary tract function and suggested that deficiency could be linked to LUTS in humans. Clinical examinations of individuals with PIEZO2 deficiency revealed that a meaningful number reported LUTS, aligning with our data indicating that men with BPH-associated BOO exhibit reduced *PIEZO2* expression. Furthermore, Marshall et al. [22] conducted experiments in *PIEZO2* knockout mice, showing that mechanosensory inputs activate PIEZO2 in urothelial cells, facilitating bladder relaxation during the filling phase, and that the absence of PIEZO2 is associated with decreased BC. This aligns with our findings, which demonstrate a positive correlation between *PIEZO2* expression and BC, suggesting that bladder smooth muscle relaxation may be compromised in *PIEZO2* knockout mice and in the detrusor muscle of patients with BOO due to reduced *PIEZO2* expression.

A recent study by Dalghi et al. [21] demonstrated that the urothelium functions as a mechanotransducer, with its activity partially dependent on the expression of *PIEZO1* or *PIEZO2*, and that ATP release from the urothelium is contingent upon PIEZO1/2. They further showed that the urothelium acts as a nonneuronal interoceptor, linking PIEZO1/2 mechanotransduction with ATP release and normal voiding function and behavior. Notably, mice lacking PIEZO1/2 exhibited overactive bladder and urinary incontinence [21]. In our study, we observed no significant differences in detrusor *PIEZO2* expression between patients with and without DO. Therefore, the evidence regarding the role of PIEZO channels in detrusor contraction is conflicting. While some studies have shown that activation of PIEZO1/2 stimulates detrusor contraction [22, 28], research by Dalghi et al. [21] indicated that *PIEZO1/2* knockout mice develop overactive bladder. Consequently, current evidence does not support the hypothesis that overexpression of urothelial *PIEZO1/2* leads to DO. Research has suggested that the biophysical properties of PIEZO channels, such as their inactivation characteristics, may be altered in certain pathological states [19]. Notably, we acknowledge the limitations of the present study, including the small sample size and the inclusion of patients with urinary retention who were using a Foley catheter. The catheter keeps the bladder in an empty state, thereby reducing the occurrence of DO, which typically depends on bladder filling. The observation that patients with BPH in retention exhibited lower *PIEZO2* expression compared to men with BPH who void spontaneously supports the hypothesis that *PIEZO2* expression is influenced by mechanical stretching. The use of an indwelling catheter keeps the bladder empty, thus preventing the mechanical stretch stress that results from DO or high-pressure detrusor voiding contractions, as seen in men with BPH who void spontaneously.

Recent research has highlighted that activation of PIEZO1, whether through specific agonists or mechanical stretching, plays a key role in the development of pathological cardiac hypertrophy [13]. This study identified PIEZO1 as a novel mechanosensor in hypertrophy induced by pressure overload. Michishita et al. found that *PIEZO1* expression in the suburothelium and detrusor increased shortly after the establishment of BOO in rats, suggesting that PIEZO1 may mediate bladder hypertrophy triggered by pressure overload [29]. One might expect PIEZO2 to play a similar role in bladder smooth muscle hypertrophy. However, our research offers a new perspective, demonstrating that men with high bladder pressures due to BPH exhibit a decrease in *PIEZO2* expression in the detrusor relative to the control group. This novel finding warrants further investigation in future studies, along with an evaluation of *PIEZO1* expression and an exploration of both *PIEZO1* and *PIEZO2* expression in the urothelium and detrusor.

The present study contributes valuable insights into *PIEZO2* expression in men with lower urinary tract dysfunction associated with BPH. To our knowledge, this is the first study to evaluate *PIEZO2* expression in this patient population. Nevertheless, several limitations must be recognized and addressed in subsequent research. First, our study was exploratory in nature, and we assessed only transcriptional regulation, even though translational regulation and activity levels are also crucial for complete analysis. In another limitation, we did not evaluate PIEZO1. As previously mentioned, our focus on PIEZO2 was influenced by the study by Marshall et al. [22], which provided evidence linking PIEZO2 deficiency to LUTS in humans. Additionally, we were unable to examine the relationship between *PIEZO2* expression and the severity and characteristics of LUTS. The predominance of urinary retention in our patient cohort precluded subgroup analyses, such as comparing patients with and without DO. Furthermore, given our small sample size and the presence of large prostates and severe BOO in our patients, we could not investigate the association between the severity of obstruction and *PIEZO2* expression. In contrast to studies utilizing animal models of obstruction, translational research in men with BPH faces limitations in selecting an appropriate control group. Our controls were cadaveric organ donors, typically healthy young individuals, who were unlikely to have experienced lower urinary tract dysfunction. We recognize the age disparity between

the BPH group and the control group as a potential confounding factor. However, obtaining bladder biopsies from age-matched men poses ethical challenges. Moreover, the high prevalence of LUTS and BPH in the older male population would require urodynamic assessments, further complicating the acquisition of control samples.

In conclusion, men with BOO resulting from BPH exhibit downregulation of *PIEZO2*, which correlates with poor BC. These findings suggest that PIEZO2 may be involved in the pathophysiology of obstruction-induced lower urinary tract dysfunction. Further research is necessary to elucidate the mechanisms and therapeutic potential of PIEZO2. However, targeting PIEZO2 could offer new strategies for managing lower urinary tract dysfunction.

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AUTHOR CONTRIBUTION STATEMENT

- Conceptualization: *CHSB, TSH, JDB Jr, KRML, AA, EB, WCN, CMG*
- Data curation: *CHSB, TSH, RP, VGS, STDR, KRML, CMG*
- Formal analysis: *CHSB, RP, VGS*
- Funding acquisition: *EB, CMG*
- Methodology: *CHSB, KRML, CMG*
- Project administration: *CHSB, CMG*
- Visualization: *CHSB*
- Writing - original draft: *CHSB, LRTDA, VGS, CMG*
- Writing - review & editing: *CHSB, LRTDA, VGS, STDR, CMG*

ORCID

Carlos Henrique Suzuki Bellucci 0000-0002-3570-859X
Luísa Resende Tenório de Albuquerque 0000-0002-4348-1321
Ruan Pimenta 0000-0002-3423-5647
Vanessa Guimarães Schreiter 0000-0003-3021-722X
Sabrina Thalita dos Reis 0000-0002-3564-3597
José de Bessa Jr 0000-0003-4833-4889
Katia Ramos Moreira Leite 0000-0002-2615-7730
Ettickan Boopathi 0000-0001-9431-7719
William C. Nahas 0000-0002-7395-8370
Cristiano Mendes Gomes 0000-0002-8486-4003

REFERENCES

1. Madersbacher S, Sampson N, Culig Z. Pathophysiology of benign prostatic hyperplasia and benign prostatic enlargement: a mini-review. Gerontology 2019;65:458-64.
2. Launer BM, McVary KT, Ricke WA, Lloyd GL. The rising worldwide impact of benign prostatic hyperplasia. BJU Int 2021;127:722-8.
3. Mirone V, Imbimbo C, Longo N, Fusco F. The detrusor muscle: an innocent victim of bladder outlet obstruction. Eur Urol 2007;5157-66.
4. Nielsen KK, Andersen CB, Petersen LK, Oxlund H, Nordling J. Morphological, stereological, and biochemical analysis of the mini-pig urinary bladder after chronic outflow obstruction and after Recovery from obstruction. Neurourol Urodyn 1995;14:269-84.
5. Damaser MS, Arner A, Uvelius B. Partial outlet obstruction induces chronic distension and increased stiffness of rat urinary bladder. Neurourol Urodyn 1996;15:650-65.
6. Bellucci CHS, Ribeiro WO, Hemerly TS, de Bessa J Jr, Antunes AA, Leite KRM, et al. Increased detrusor collagen is associated with detrusor overactivity and decreased bladder compliance in men with benign prostatic obstruction. Prostate Int 2017;5:70-4.
7. Fusco F, Creta M, De Nunzio C, Iacovelli V, Mangiapia F, Li Marzi V, et al. Progressive bladder remodeling due to bladder outlet obstruction: a systematic review of morphological and molecular evidences in humans. BMC Urol 2018;18:15.
8. Coplen DE, Macarak EJ, Howard PS. Matrix synthesis by bladder smooth muscle cells is modulated by stretch frequency. In Vitro Cell Dev Biol Anim 2003;39:157-62.
9. Ranade SS, Syeda R, Patapoutian A. Mechanically activated ion channels. Neuron 2015;87:1162-79.
10. Galvin DJ, William R, Watson G, Gillespie JI, Brady H, Fitzpatrick JM. Mechanical stretch regulates cell survival in human bladder smooth muscle cells in vitro. Am J Physiol Renal Physiol 2002;283:F1192-9.
11. Barbosa JABA, Reis ST, Nunes M, Ferreira YA, Leite KR, Nahas W, et al. The obstructed bladder: expression of collagen, matrix metal-

loproteinases, muscarinic receptors, and angiogenic and neurotrophic factors in patients with benign prostatic hyperplasia. Urology 2017;106:167-72.
12. Tamura I, Rosenbloom J, Macarak E, Chaqour B. Regulation of Cyr61 gene expression by mechanical stretch through multiple signaling pathways. Am J Physiol Cell Physiol 2001;281:C1524-32.
13. Zhang Y, Su SA, Li W, Ma Y, Shen J, Wang Y, et al. Piezo1-mediated mechanotransduction promotes cardiac hypertrophy by impairing calcium homeostasis to activate calpain/calcineurin signaling. Hypertension 2021;78:647-60.
14. Boopathi E, Gomes C, Zderic SA, Malkowicz B, Chakrabarti R, Patel DP, et al. Mechanical stretch upregulates proteins involved in Ca 2 sensitization in urinary bladder smooth muscle hypertrophy. Am J Physiol Cell Physiol 2014;307:542-53.
15. Yamaguchi O. Response of bladder smooth muscle cells to obstruction: signal transduction and the role of mechanosensors. Urology 2004;63(3 Suppl 1):11-6.
16. Sjuve Scott R, Li Z, Paulin D, Uvelius B, Small J, Arner A. Role of desmin in active force transmission and maintenance of structure during growth of urinary bladder. Am J Physiol Cell Physiol 2008; 295:324-31.
17. Inui E, Ochiai A, Naya Y, Ukimura O, Kojima M. Comparative morphometric study of bladder detrusor between patients with benign prostatic hyperplasia and controls. J Urol 1999;161:827-30.
18. Coste B, Mathur J, Schmidt M, Earley TJ, Ranade S, Petrus MJ, et al. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. Science 2010;330:55-60.
19. Li X, Hu J, Zhao X, Li J, Chen Y. Piezo channels in the urinary system. Exp Mol Med 2022;54:697-710.
20. Dalghi MG, Clayton DR, Ruiz WG, Al-Bataineh MM, Satlin LM, Kleyman TR, et al. Expression and distribution of PIEZO1 in the mouse urinary tract. Am J Physiol Renal Physiol 2019;317:303-21.
21. Dalghi MG, Ruiz WG, Clayton DR, Montalbetti N, Daugherty S, Beckel J, et al. Functional roles for PIEZO1 and PIEZO2 in urothelial mechanotransduction and lower urinary tract interoception. JCI Insight 2021;6:e152984.
22. Marshall KL, Saade D, Ghitani N, Coombs AM, Szczot M, Keller J, et al. PIEZO2 in sensory neurons and urothelial cells coordinates urination. Nature 2020;588:290-5.
23. Xiao B. Levering mechanically activated piezo channels for potential pharmacological intervention. Annu Rev Pharmacol Toxicol 2020:60:195-218.
24. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. BJU Int 1999;84:14-5.
25. D'Ancona C, Haylen B, Oelke M, Abranches-Monteiro L, Arnold E, Goldman H, et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn 2019;38: 433-77.
26. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2-ΔΔCT method. Methods 2001;25:402-8.
27. Bagriantsev SN, Gracheva EO, Gallagher PG. Piezo proteins: regulators of mechanosensation and other cellular processes. J Biol Chem 2014;289:31673-81.
28. Miyamoto T, Mochizuki T, Nakagomi H, Kira S, Watanabe M, Takayama Y, et al. Functional role for Piezo1 in stretch-evoked Ca2+ influx and ATP release in Urothelial cell cultures. J Biol Chem 2014; 289:16565-75.
29. Michishita M, Yano K, Tomita KI, Matsuzaki O, Kasahara KI. Piezo1 expression increases in rat bladder after partial bladder outlet obstruction. Life Sci 2016;166:1-7.