Published in final edited form as:

Urology. 2007 September ; 70(3): 487–492.

Physiological Reactivity to a Laboratory Stress Task among Men with Benign Prostatic Hyperplasia

Philip M. Ullrich, Ph.D.¹, Susan K. Lutgendorf, Ph.D.², and Karl J. Kreder, M.D.³

¹ *Department of Rehabilitation Medicine, University of Washington*

² *Departments of Psychology and Obstetrics and Gynecology, University of Iowa*

³ *Department of Urology, University of Iowa*

Abstract

Objectives—The sympathetic nervous system (SNS) and hypothalamic-pituitary-gonadal (HPG) axis are involved in the pathophysiology of benign prostatic hyperplasia (BPH). The SNS and HPG axis are also highly reactive to psychological stressors, yet associations between prostate function and reactivity to a psychological stressor have not been examined utilizing standardized psychological stress paradigms. The objective of this study was to examine associations between psychological stress reactivity and BPH disease parameters.

Methods—83 men diagnosed with BPH completed a standardized laboratory stress task yielding measures of blood pressure, testosterone, and cortisol reactivity. Links were examined between stress reactivity (as indicated by change in blood pressure, testosterone, and cortisol during a stress task) and measures of BPH disease including prostate volumes, post-voiding residual volume, urine flow rates, self-reported lower urinary tract symptoms (LUTS), impact and bother scores.

Results—In equations controlling for BPH medications, BMI, and age, greater diastolic blood pressure reactivity was associated with higher transitional zone ($p < .001$), higher total prostate gland volume ($p < .05$), higher residual urine volume ($p < .05$), more severe LUTS ($p < .001$), and greater impact scores ($p < .05$). Greater cortisol reactivity was associated with higher bother ($p < .05$) and impact scores ($p < .001$).

Conclusions—Physiological reactivity to a standardized laboratory stressor is associated with objective and subjective BPH disease parameters. These findings contribute to a growing literature suggesting that stress conditions may be associated with the development or aggravation of prostatic disease.

Keywords

Stress; prostatic hyperplasia; prostate; testosterone; cortisol

Benign prostatic hyperplasia (BPH) is associated with troublesome lower urinary tract symptoms (LUTS) caused by the growth and increased contractility of the prostate.¹ Both the hypothalamic-pituitary-gonadal (HPG) axis and the sympathetic nervous system (SNS) are thought to have causal roles in the etiology of this syndrome.^{1, 2} In parallel research,

Correspondence including requests for reprints should be addressed to: Phil Ullrich, Ph.D., Department of Rehabilitation Medicine, box 359740, Harborview Medical Center, 325 Ninth Ave, Seattle, WA, 98104. Phone: 206-277-3911. Fax: 206-764-2935. Electronic mail: pullrich@u.washington.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

psychological factors such as stress have been shown to have considerable influence over the SNS and HPG axis,³ suggesting the hypothesis that psychological stress may be linked to prostatic disease. Preliminary support for this hypothesis is growing. Stone and colleagues⁴ found that elevated stress was prospectively associated with higher prostate specific antigen levels among a sample of healthy men. Lifetime stress has been associated with prostate volume and post-void residual volumes among men with BPH.⁵ Sympathetic nervous system overactivity, a routine correlate of psychological stress, has also been associated with BPH disease parameters in epidemiological and laboratory studies.^{6, 7} To further explore links between psychological stress and BPH, this study examined associations between physiological responses to a standardized laboratory stressor and parameters of BPH using data gathered in an ancillary study to the Medical Therapy of Prostatic Symptoms (MTOPS) trial.⁸ It was hypothesized that SNS and HPG axis responses to a standardized psychological stressor would relate to BPH disease parameters, with greater reactivity associated with worse disease. Reactivity to laboratory stressors has been associated with chronic stress conditions^{9,10} and real-world reactions to stress, ambulatory blood pressure, and clinical outcomes.¹¹

METHODS

Participants

Participants were recruited from a population of 119 patients with BPH involved at one site in the MTOPS clinical trial (detailed elsewhere).⁸ The MTOPS trial was an NIH-funded multi-site study investigating the efficacy of two drugs (finasteride and doxazosin) used to treat BPH. Finasteride is a 5-alpha reductase inhibitor that interrupts the conversion of testosterone to DHT. Doxazosin is an alpha blocker that inhibits the effects of epinephrine and norepinephrine on the prostate. Participants were randomly assigned to receive doxazosin, finasteride, both, or placebo. Eligibility criteria included age 50+ years, urinary flow rate 4–15 ml/sec, and American Urological Association (AUA) urinary symptom score 8–30. Exclusion criteria for the MTOPS trial were prior prostate treatment, psychiatric diagnosis, history of alcohol or substance abuse, current hormonal treatment, PSA over 10ng/mL, recent heart attack or stroke, cancer, prior pelvic surgery, neurologic conditions, or bacterial prostatitis.

Participants in the MTOPS trial were recruited beginning in 1994 and were prescribed finasteride/placebo and doxazosin/placebo to be taken once daily during the seven year trial. Prostate volumes, urine flow, urinary retention, and ratings of LUTS were collected at baseline and at annual follow-ups. Patients attended their final follow-up appointment for the trial in 2001, and were recruited for the ancillary study at this time. The Institutional Review Board of the University of Iowa approved all ancillary study procedures.

Ancillary study protocol

After giving informed consent for the ancillary study, participants completed MTOPS measures including: transrectal ultrasound of prostate volume, urine flow rates, post-void residual bladder volumes, and a questionnaire. Thereafter, participants began ancillary study procedures.

Participants were seated in a chair and a blood pressure cuff was placed on the right arm. Participants rested in this position for five minutes while completing the questionnaire. Thereafter, two baseline blood pressure measurements were taken, 2 minutes apart. Also, participants gave saliva samples for measuring testosterone and cortisol. Following the rest period, participants completed a standardized stress task as follows. Participants were instructed to prepare a speech defending themselves against alleged shoplifting for two minutes, after which they delivered the speech for three minutes in front of a video camera. Blood pressure was measured every two minutes throughout the speech task. The speech task

is described elsewhere in detail.¹² Following the speech task, participants rested for 20 minutes and then gave additional salivary samples for measuring testosterone and cortisol. Elevations in salivary testosterone and cortisol can be observed 15 to 20 minutes following a stressor.^{13, 14}

Blood pressure

Systolic and diastolic blood pressures were recorded with a Critikon Dinamap Plus vital signs monitor attached to the dominant arm. Blood pressure was measured every two minutes throughout the speech stressor. Changes between the baseline and the mid-stressor measures served as indices of stress reactivity.

Salivary testosterone and cortisol

Testosterone measurements were taken from unstimulated whole saliva collected in assay tubes by passive drool and then frozen until assayed. Saliva samples were assayed for testosterone using an enzyme immunoassay specifically designed for use with saliva according to the manufacturer's procedures (Salimetrics, State College, PA). Saliva sampling for cortisol measurements was performed using small swabs chewed by participants for 60 seconds. Changes between baseline and post-stressor measures of salivary cortisol and testosterone served as indicators of reactivity to the stress tasks in analyses.

Urine flow rates and postvoiding residual volume (PVR)

Prior to beginning ancillary study procedures, participants voided their bladders into a Dantec Urolynx 1000 flowmeter, automatically measuring maximum and mean flow rates. PVR bladder volume was assessed following urine flow measurements using the Bladderscan BVI 2000 portable ultrasound unit according to manufacturer's guidelines. PVR bladder volumes were automatically calculated by the ultrasound device.

Prostate volume

Prostate volume was measured by transrectal ultrasound using the Bruel & Kjaer Model #8551 multi-plane transducer. In this measurement, an ultrasound probe is inserted rectally and images of prostate height, width, and length are obtained. Transitional zone (TZ) and total prostate volume is calculated.

Lower urinary tract symptoms (LUTS)

LUTS was measured using the AUA-7 Symptom index.¹⁵ The AUA-7 is a 7-item questionnaire measuring the frequency of clinically important urinary symptoms (emptying, frequency, intermittency, urgency, weak stream, hesitancy, nocturnal polyuria). The frequency of each symptom during the past month is rated on a 6-point scale ranging from "not at all" to "almost always". Ratings are summed to give a total symptom score ranging from 0 to 35.

Impact and bother

The degree to which men were bothered by their urinary symptoms was assessed using the bother question administered as part of the AUA symptom index.¹⁵ Respondents indicate how bothersome their symptoms have been in the past month from "not at all" to "a lot", generating a score from 0 to 3. This question has demonstrated validity and reliability among men with BPH¹⁶. The BPH Impact index¹⁷ was used to measure the extent of functional interference due to symptoms. The BPH Impact index generates scores from 0 to 13 with higher scores reflecting greater impact. The BPH Impact index has good internal consistency and validity as demonstrated by associations with relevant constructs¹⁷.

Statistical analyses

Pearson correlations were used to examine simple associations between study variables. Repeated measures ANCOVAs were used to examine the effect of the laboratory stressor, and medication influence on reactivity. MTOPS treatment group was converted into three dummy variables to serve as a control variable in regression analyses. Hierarchical multiple regression procedures were used to examine hypothesized associations between study variables. All models adjusted for age, BMI, and MTOPS treatment group. Baseline reactivity measures were entered into the equations in the second step. In the third step of each equation, the post-stressor reactivity measure was entered as the main predictor of interest. With baseline reactivity measures statistically controlled in the second step of the equation, the post-stressor reactivity measure represented stressor-related change. Bonferroni corrections were used to account for multiple comparisons.

RESULTS

Sample Characteristics

Of the 119 MTOPS patients available for recruitment, 83 (70%) agreed to participate in the ancillary study. The distribution of participants across MTOPS study groups closely approximated the proportions found in the entire sample. The majority of participants were retired, married, and educated beyond high school. The mean age of the sample was 68 and all participants were Caucasian. Table 1 shows descriptive statistics for key study variables.

Reactivity measures

Patients taking doxazosin tended to have lower diastolic [$F(1, 81) = 6.23, p < .05$] and systolic blood pressure [$F(1, 81) = 20.47, p < .001$] than patients not taking doxazosin across baseline and post-stress measures. However, medication groups were not significantly different on change in systolic or diastolic blood pressure. To control for possible effects of doxazosin, significant analyses were repeated using only patients not taking doxazosin, yielding comparable results in terms of direction and magnitude of associations. Repeated measures ANCOVAs revealed significant increases between baseline and the speech stressor on both diastolic [$F(1, 81) = 88.61, p < .001$] and systolic [$F(1, 81) = 127.31, p < .001$] blood pressure, indicating that the speech task elicited a stress reaction. Medication group was not associated with testosterone or cortisol baseline, post-stress, or reactivity measures (all $ps > .20$). Testosterone increased between baseline and post-stress measures [$F(1, 81) = 3.91, p < .05$]. However, salivary cortisol levels did not significantly change between baseline and post-stress measures.

Primary analyses

LUTS was not correlated with objective measures including urine flow rates, PVR, prostate volumes. In bivariate correlations between reactivity measures and BPH parameters, DBP reactivity was significantly associated with total prostate volume, TZ volume, mean urine flow, residual urine volume, LUTS, and bother. Cortisol reactivity was associated with bother and impact scales. See Table 2. Using Bonferroni corrections to adjust for multiple comparisons, DBP remained significantly associated with TZ volume and LUTS, and cortisol reactivity remained significantly associated with impact. Similar results were found using regression models controlling for age, BMI, and medication group. In these regression models, DBP reactivity was significantly associated with greater TZ volume, greater total prostate gland volume, higher impact scores, residual volumes, and more severe LUTS (all $ps < .05$). Figure 1 depicts total prostate gland volume results. Greater cortisol reactivity was associated with higher bother and impact scores. Using Bonferroni corrections to adjust for multiple comparisons, DBP reactivity remained significantly associated with TZ volume and LUTS,

and cortisol reactivity was significantly associated with impact scores. Other associations between reactivity measures and BPH variables were insignificant.

DISCUSSION

Psychological stress has long been cited as a possible contributor to the exacerbation or persistence of urological complaints.¹⁸ Present results associating DBP and cortisol reactivity with BPH disease factors are generally comparable to prior reports^{6,7} and inferentially support a possible effect of psychological stress on BPH. Our study design makes it difficult to elucidate cause-effect interpretations of associations between stress reactivity and BPH disease factors. However, present results represent an addition to a growing body of empirical literature documenting that stress-related conditions may be closely related to prostatitic disease factors.¹⁹

There are a number of plausible explanations for mechanisms underlying associations between stress reactivity and BPH parameters. One possibility is that stress-related SNS overactivity decreases the rate of cell apoptosis, resulting in greater total prostate cell proliferation. In support of this argument, rat models have demonstrated interactions between SNS activity and prostate growth. Administration of medications that inhibit the binding of norepinephrine to alpha receptors results in increased apoptotic activity and lower total prostate cell proliferation.²⁰ Moreover, severance of sympathetic nerves innervating the prostate results in decreased prostate weight.²¹

Associations between stress reactivity and LUTS might be explained by the influence of stress on prostate contractility and pelvic floor muscle tension. The tension of prostatic smooth muscle is mediated by alpha-adrenoreceptors that are stimulated by epinephrine and norepinephrine,² substances released in response to acute stressors.³ Administration of exogenous epinephrine and norepinephrine results in the contraction of the prostate.²² It has also been posited that stress reactions increase the muscular tension in the pelvic floor²³, resulting in voiding symptoms.

Finally, it is possible that insulin may mediate associations between stress and BPH disease. Short-term²⁴ and chronic stressors²⁵ have been associated with elevated insulin levels. Furthermore, hyperinsulinemia may promote prostate growth^{7,26}. Possible pathways linking stress and insulin to prostatic function may be especially apparent among men experiencing metabolic syndrome²⁷, who experience increased reactivity to stress in the SNS and hypothalamic-pituitary-adrenal axis²⁸.

Cortisol reactivity was associated with subjective measures of urinary bother and functional interference yet not with objective BPH parameters. This finding is consistent with past research associating increased cortisol with stress responses that involve emotional distress.³ Furthermore, increased psychological distress is associated with elevated somatic complaints²⁹ including LUTS³⁰. The implication is that the degree to which patients experience psychological distress in reaction to stressors may relate to how they perceive or respond to urinary symptoms²⁹.

We should note that the cross-sectional, correlational design of the study precludes confident statements regarding the direction and nature of associations between study variables. Although numerous arguments have been made suggesting that psychological factors may have impacted measures of urological function, it is conceivable that urological functioning may have influenced reactivity to the laboratory stressor through the mediating influence of urological symptoms. In other words, urological dysfunction could be expected to cause discomfort due to LUTS, with consequential elevations in stress reactivity. However, objective measures of urological disease were not associated with urological symptoms. This does not

support a model in which stress reactivity is influenced by factors such as prostate volume or PVR. It is not clear how objective measures of urological functioning may have affected stress reactivity independent of urological symptom perception.

CONCLUSIONS

Physiological reactivity to a standardized laboratory stressor was associated with objective and subjective BPH disease parameters, raising interesting possibilities regarding the relevance of stress in BPH. Stress and other psychological factors may interact with anatomic and biological factors to influence disease etiology. Stress may also be considered one of a number of factors with possible influence over the waxing and waning of BPH signs and symptoms.

Acknowledgements

The authors gratefully acknowledge the assistance of Margery Fearing, RN, and Nathan Miller, BS, in conducting this study. This study was funded by NIH grant # DK49971 awarded to the third author (KJK).

References

1. Lee CL, Kozlowski JM, Grayhack JT. Etiology of benign prostate hyperplasia. *Urol Clin North Am* 1995;22:237–246. [PubMed: 7539172]
2. Lepor H. Alpha blockage for the treatment of benign prostatic hyperplasia. *Urol Clin North Am* 1995;22:375–386. [PubMed: 7539182]
3. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. *JAMA* 1992;267:1244–1252. [PubMed: 1538563]
4. Stone AA, Mezzacappa ES, Donatone BA, Gonder M. Psychosocial stress and social support are associated with prostate-specific antigen levels in men: Results from a community screening program. *Psychosom Med* 1999;18:482–486.
5. Ullrich PM, Lutgendorf SK, Leserman J, Kreder KJ. Stress, Hostility, and Disease Parameters of Benign Prostatic Hyperplasia. *Psychosom Med* 2005;67:476–482. [PubMed: 15911913]
6. McVary KT, Rademaker A, Lloyd GL, Gann P. Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 2005;174:1327–1333. [PubMed: 16145413]
7. Hammarsten J, Hogstedt B. Clinical, anthropometric, metabolic and insulin profile of men with fast annual growth rates of benign prostatic hyperplasia. *Blood Pressure* 1999;8:29–36. [PubMed: 10412880]
8. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL, Dixon CM, Kusek JW, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349:2387–2398. [PubMed: 14681504]
9. Kamarck TW, Schwartz JE, Janicki DL, Shiffman S, Raynor DA. Correspondence between laboratory and ambulatory measures of cardiovascular reactivity: A multilevel modeling approach. *Psychophysiology* 2003;40:675–683. [PubMed: 14696722]
10. Fleming I, Baum A, Davidson LM. Chronic stress as a factor in physiological reactivity to challenge. *Health Psychol* 1987;6:221–237. [PubMed: 3595547]
11. Sherwood, A.; Turner, JR. *Individual Differences in Cardiovascular Responses to Stress*. Plenum Press; New York, NY: 1992. A conceptual and methodological overview of cardiovascular reactivity research; p. 3-32.
12. Saab PG, Matthews KA, Stoney CM, McDonald RH. Premenopausal and postmenopausal women differ in their cardiovascular and neuroendocrine responses to behavioral stressors. *Psychophysiology* 1989;26:270–280. [PubMed: 2756076]
13. Dabbs JM. Testosterone measurements in social and clinical psychology. *J Soc Clin Psych* 1992;11:302–321.
14. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: Recent developments and applications. *Psychoneuroendocrinology* 1994;19:313–333. [PubMed: 8047637]

15. Barry MJ, Fowler FJ, O'Leary MP, et al. for the Measurement Committee of the American Urological Association. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol* 1992;148:1549–1564. [PubMed: 1279218]
16. O'Leary MP. Validity of the "Bother score" in the evaluation and treatment of symptomatic benign prostatic hyperplasia. *Rev Urol* 2005;7(1):1–10. [PubMed: 16985801]
17. Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK. Measuring disease-specific health status in men with benign prostatic hyperplasia. *Med Care* 1995;33(4):145–155. [PubMed: 7837823]
18. Eyres HM. Nervous retention of urine. *BMJ* 1912;1:484–487.
19. Pontari MA, Ruggieri MR. Mechanisms in prostatitis/chronic pelvic pain syndrome. *J Urol* 2004;172:839–845. [PubMed: 15310980]
20. Kyprianou N, Chon J, Benning CM. Effects of alpha-adrenoreceptor (alpha1-AR) antagonists on cell proliferation and apoptosis in the prostate: Therapeutic implications in prostatic disease. *Prostate* 2001;S9:42–46.
21. McVary KT, Razzaq A, Lee C, Venegas MF, Rademaker A, McKenna KE. Growth of the rat prostate gland is facilitated by the autonomic nervous system. *Biol Reprod* 1994;51:99–107. [PubMed: 7918880]
22. Lepor H, Gup DI, Baumann M. Laboratory assessment of terazosin and alpha1 blockade in prostatic hyperplasia. *Urology* 1988;32:21–24. [PubMed: 2462301]
23. Straub LR, Ripley HS, Wolf S. Disturbance of bladder function associated with emotional states. *JAMA* 1949;141:1139–1143.
24. Alvarez MA, Portilla L, Gonzalez IB, Ezcurra E. Insulin response to a short stress period. *Psychoneuroendocrinology* 1989;14:241–244. [PubMed: 2667017]
25. Raikkonen K, Keltikangas J, Hautanen A. The role of psychological coronary risk factors in insulin and glucose metabolism. *J Psychosom Res* 1994;38:705–713. [PubMed: 7877125]
26. Hammarsten J, Högstedt B. Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. *Eur Urol* 2001;39:151–158. [PubMed: 11223674]
27. Bjorntorp P. Abdominal obesity and the metabolic syndrome. *Ann Med* 1992;13:465–468. [PubMed: 1485940]
28. Bjorntorp P. Body fat distribution, insulin resistance, and metabolic disease. *Nutrition* 1997;13:795–803. [PubMed: 9290093]
29. Watson D, Pennebaker JW. Health complaints, stress, and distress: Exploring the central role of negative affectivity. *Psych Rev* 1989;96:234–254.
30. Welch G, Weinger K, Barry MJ. Quality-of-life impact of lower urinary tract symptom severity: results from the Health Professionals Follow-up Study. *Urology* 2002;59(2):245–250. [PubMed: 11834396]

Figure 1.
Association Between DBP Reactivity and Total Prostate Volume.

Table 1

Means and standard deviations of key study variables.

Variable	Mean (SD)
Testosterone base (pg/mL)	90.13 (40.22)
Testosterone post-stressor (pg/mL)	97.95 (42.61)
Cortisol base (nmol/L)	14.96 (12.55)
Cortisol post-stressor (nmol/L)	13.50 (9.23)
DBP, base (mm/Hg)	77.39 (10.57)
DBP, stressor (mm/Hg)	86.51 (8.49)
SBP, base (mm/Hg)	126.68 (14.49)
SBP, stressor (mm/Hg)	141.91 (10.87)
LUTS score	10.93 (6.06)
Maximum urine flow (mL/sec)	13.26 (5.80)
Mean urine flow (mL/sec)	7.09 (2.92)
Post-void Residual Volume (mL)	40.99 (70.57)
Transition Zone volume (mL)	8.64 (6.69)
Prostate volume (mL)	28.44 (15.21)

Notes: DBP, diastolic blood pressure; LUTS, lower urinary tract symptoms; mm/Hg, millimeters of mercury; mL/sec, milliliters per second; mL, milliliters; nmol/L, nanomoles per liter; pg/mL, picograms per milliliter; SBP, systolic blood pressure.

Table 2

Bivariate correlations between reactivity measures and BPH parameters.

	DBP	SBP	Test	Cort
Total Prostate Volume	.22 [*]	.09	.10	.08
Trans-zone Prostate Volume	.44 ^{***}	.00	.08	.06
Max flow	-.20	-.13	.17	.06
Mean flow	-.22 [*]	-.11	.21	.14
Residual	.33 ^{**}	.12	.05	.06
LUTS	.39 ^{***}	.14	.00	.08
Bother	.15	.04	.05	.31 ^{**}
Impact	.32 ^{**}	.11	.04	.37 ^{***}

Notes: $p < .05$,^{**}
 $p < .01$,^{***}
 $p < .001$. Bother, urinary bother symptoms; Cort, change in cortisol; DBP, change in diastolic blood pressure; Impact, impact of urinary symptoms; LUTS, lower urinary tract symptoms; Max and mean flow, urinary flow rates; residual, residual urine volume; SBP, change in systolic blood pressure; Test, change in testosterone.