271

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LONGITUDINAL CHANGES IN ISOVOLUMETRIC BLADDER PRESSURE IN RESPONSE TO AGE RELATED PROSTATE GROWTH IN 1020 HEALTHY MALE VOLUNTEERS

Hypothesis / aims of study

Benign prostatic enlargement (BPE) is an age-related process, which has been described in numerous community based studies. However, only a few of these are longitudinal and in none of these the urinary bladder response to the increasing urethral resistance was studied. The most important reason for this lack of information is that invasive pressure flow studies are needed to quantify bladder contractility. With the recently developed condom catheter method the isovolumetric bladder pressure, which is a measure for bladder contractility, can be determined noninvasively. We have applied this method in a longitudinal study of 1020 healthy male volunteers to study the urinary bladder response to BPE.

Study design, materials and methods

Between 2001 and 2010 1020 male volunteers underwent 3 non-invasive study sessions. Volunteers were included if aged 38 to 77 years, and able to continuously void in a standing position with a minimum flow rate of 5.4 ml/s, had had no history of heart condition, no treatment or surgery of the lower urinary tract (LUT) and no other disease that could affect urinary bladder function, and signed informed consent. LUT symptoms (LUTS) were not an exclusion criterion. The first study session took place between 2001 and 2003, the second between 2004 and 2006, and the third between 2006 and 2010. Each session consisted of 3 voidings: one into a uroflowmeter to determine the maximum free flow rate (Q_{max}) and two through the condom catheter. Voiding through the condom catheter was repeatedly interrupted to measure the maximum pressure in the condom ($P_{cond.max}$), which represents the maximum isovolumetric bladder pressure [1]. Before the first voiding, the prostate volume (PV) was determined by transabdominal ultrasonography (Aloka SSD-900, 3.5 MHz probe). The volunteers were also asked to complete the IPSS questionnaire. For data analysis, the volunteers were stratified in five year age groups based on their age at inclusion. Data were presented as mean with 95% confidence interval, except IPSS which was, being non-parametric, presented as median with 95% confidence interval. Longitudinal changes in the age groups during the 5 years follow up were analyzed using mixed model analysis (SAS®). PV, Q_{max} and IPSS were log transformed for data analysis.

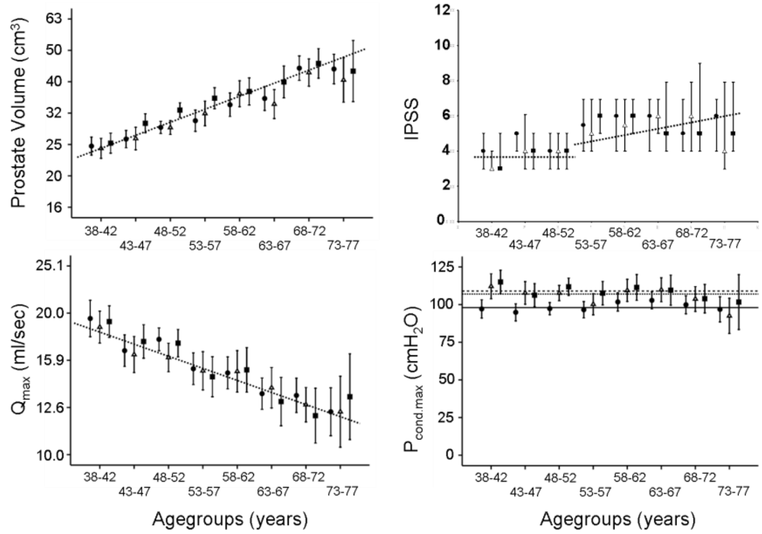
Results

Transverse analysis of PV showed an increase with increasing age in each study round. Longitudinal analysis showed a small but significant increase from the second to the third study round of 5%. Ignoring this small difference, the relation between PV and age was described by one equation: log(PV) = 0.008*age + 1.045 (see figure below). For Q_{max}, both first and second round showed a small but significant different dependency on age of only 3.5% compared to the third study round. Again, the relation between Q_{max} and age was described by one equation: log(Q_{max}) = -0.005*age + 1.478. IPSS did not depend on age when volunteers were younger than 55 years (median IPSS score 3.7). Above 55 years, IPSS increased with age (log(IPSS+1) = 0.005*age + 0.475). For $P_{cond.max}$ an opposite result was found. In all 3 study rounds there was no significant difference between the age groups. However, there was a significant difference between the 3 study rounds, resulting in 3 different horizontal lines: the following regression equations were calculated: $P_{cond.max – round 1}$ = 98, $P_{cond.max – round 2}$ = 107. $P_{cond.max – round 3}$ = 109.

Interpretation of results

Several longitudinal community based studies have shown evidence that with increasing age PV and IPSS increase, whereas Q_{max} decreases. In our study similar age dependent changes in PV, Q_{max} and IPSS were found. At 55 years of age, there was a sudden increase in IPSS in our volunteers. This may have been caused by cardiac decompensation, causing nocturia. This is supported by the finding that urine production during the night also suddenly increased from 41ml/hr in the age group 48-52 years to 56 ml/hr in the age group 53-57 years in the same group of volunteers [2]. Although in the figure the IPSS above 55 years of age does not seem to be age-dependent, statistical analysis showed an increase in IPSS score of 1% per year. In the figure, the symbols represent the median of all measured data. However, in the statistical analysis by SAS® missing values in the third round were predicted by extrapolation based on the data from the first and second round. As the volunteers that dropped out had significantly higher IPSS scores in the second study round (data not shown), this results in higher predicted IPSS scores for the third round.

Our study also shows that the average bladder contractility was not significantly different between the age groups, but increased during the five year longitudinal study period in each age group. Our first hypothesis is that the longitudinal pressure rise represents compensation of the urinary bladder triggered by the increasing urethral resistance due to age related BPE. Based on this pressure increase during the longitudinal observation of the volunteers in the five year study interval, one would expect the pressure to increase with the age group as well. However, between the age groups, the pressures were very similar during the follow up period. Our second hypothesis is that this must be explained by selection. In guinea pigs it has been shown that along with an increase in urethral resistance, contractility increased significantly up to a certain maximum and then decreased again. This pattern was apparent in all animals, although the individual response rate varied [3]. In human males the onset of prostatic obstruction is not well defined. The increase in urinary bladder contractility found in age group 1 (38-42 years) shows that already at the age of 40 the average bladder contractility rose noticeably. By the time such early responders reach the age of 45 they probably have developed symptoms, and have sought for help, resulting in treatment which rules out inclusion in the study. An additional indication for this interpretation is that in all age groups the upper limit of the confidence interval of contractility is approximately the same. At even higher contractility symptoms get serious and treatment starts, preventing inclusion in the study.



PV, Q_{max}, IPSS and $P_{cond.max}$ were plotted against the 8 groups of age at inclusion. Closed circles represent the first, open triangles the second and closed squares the third study round. PV, Q_{max} and $P_{cond.max}$ are presented as mean and 95% confidence intervals. IPSS is presented as median and 95% confidence interval. Lines represent the regression lines derived by the mixed model analysis (SAS®).

For $P_{cond.max}$ the 3 horizontal lines represent the 3 study rounds (study round 1 = drawn line, study round 2 = dotted line, study round 3 = dashed line).Note that PV and Q_{max} are shown on a log scale vertical axis.

Concluding message

In conclusion, with increasing age PV and IPSS increased, whereas Q_{max} decreased. Isovolumetric bladder pressure increased during the 5 years longitudinal follow up, but not in a transverse analysis of the different age groups, possibly caused by compensation of the urinary bladder resulting in a selection effect. The condom catheter method is a straightforward and patient-friendly method to measure bladder contractility in non-invasive longitudinal studies, resulting in a high response rate.

References

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3. J Urol 164:1021-1024 (2000)

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Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Medical Ethical Committee Erasmus MC**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**