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H.-J. Yu · R. M. Levin · P. A. Longhurst · M. S. Damaser

Ability of obstructed bladders to empty is dependent on method of stimulation

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Abstract *Purpose:* To correlate pharmacologic changes that occur in the bladder after a partial outlet obstruction with the bladder's ability to perform work and empty.
Methods: After 2 weeks of partial outlet obstruction, rabbit bladders were stimulated in vitro both isovolumetrically [field stimulation (FS)] and to empty (FS, bethanechol, and KCl).
Results: The obstructed bladders were separated into two groups according to their ability to empty when stimulated with FS. Compensated bladders were those that could empty as much as controls. Decompensated bladders emptied significantly less than controls. With FS and bethanechol, the compensated obstructed bladders showed no difference from the control bladders in their ability to empty. In contrast, with KCl, the compensated bladders generated significantly less pressure, performed less work, and emptied less than controls. When the decompensated bladders were stimulated with all three types of stimulation, all parameters, including emptying ability, were significantly decreased.
Conclusions: The reduction in the response of compensated bladders to KCl stimulation suggested that the initial defects to the bladder after an outlet obstruction involved the interaction of smooth muscle proteins with calcium and ATP. In contrast, the response of decompensated bladders to all three forms of stimulation was equally reduced, suggesting that the degenerative processes were directly related to significant cellular damage to metabolic processes involved in energy synthesis, storage, and utilization.

Key words Bladder · Obstruction · Stimulation · Rabbit · Function · Work

H.-J. Yu · R. M. Levin[1] · P. A. Longhurst[1,2] · M. S. Damaser[3,4] (✉)
Division of Urology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

H.-J. Yu
Departments of Physiology and Urology,
Medical College of National Taiwan University, Taipei, Taiwan

R. M. Levin
Philadelphia VA Medical Center, Philadelphia, PA, USA

Current address:
[1]Albany College of Pharmacy, Albany, NY, USA

[2]Division of Urology, Albany Medical College,
Albany, NY, USA

(✉) [3]Rehab R&D Center (151L), Hines VA Hospital,
P.O. Box 20, Hines, IL 60141, USA

[4]Department of Urology, Loyola University Medical Center,
Maywood, IL, USA

Urinary bladder outlet obstruction is a common medical problem. The majority of males aged 50–60 years and older have various degrees of bladder outlet obstruction secondary to benign prostatic hyperplasia (BPH) [10, 45]. In addition to clinical studies, several animal models of partial outlet obstruction have been developed in order to understand the effects of outlet obstruction on bladder morphology, physiology, and pharmacology [16, 36]. In the rabbit, bladder dysfunction after partial outlet obstruction has been separated into two distinct categories: compensated and decompensated bladder function. Compensated bladders are characterized by a relatively stable bladder mass, near normal pressure generation, and nearly complete emptying in response to stimulation. Decompensated bladders are characterized by a progressive increase in bladder mass, progressive decreases in the responses to all forms of stimulation, and an inability to empty [24, 27].

The amount of mechanical work the bladder does during emptying could indicate the extent of bladder dysfunction [2, 6]. In addition, several alternative methods for determining the strength of bladder contraction using bladder work factors have been proposed [1, 11, 30, 43]. We have chosen to study the ability of the bladder to empty by calculating external mechanical power and work. These parameters provide an accurate and straightforward method to analyze bladder strength during emptying.

The isolated whole bladder model affords us the opportunity to study the characteristics of bladder pressure generation and emptying in a well-defined system without the influence of either neuronal reflexes or urethral tension [19]. In addition, it enables us to use different methods to stimulate the bladder, including field stimulation (FS), which excites the parasympathetic nerves of the bladder, bethanechol, which stimulates cholinergic receptors directly, and KCl, which depolarizes the smooth muscle membrane. The current study was designed to investigate the effect of these three stimulation methods on the ability of obstructed bladders to generate mechanical work and empty.

Material and methods

Creation of obstruction

Partial bladder outlet obstructions were created in 17 male New Zealand White rabbits (Hazelton Farms). The rabbits were anesthetized with 25 mg ketamine and 10 mg xylazine i.m. Surgical anesthesia was maintained with pentobarbital (25 mg/kg i.v.). Under sterile conditions, the urinary bladder was catheterized with an 8-Fr. Foley catheter and the bladder exposed through a midline incision. Partial outlet obstruction was initiated by placing a 3–0 silk ligature loosely around the catheterized urethra. The catheter was removed and the incision closed with 3–0 silk. The obstructed rabbits were evaluated at 14 days of obstruction.

Five male and six female non operated age-matched rabbits were used as controls. There were no significant differences in any parameter studied between the male and female controls, so these are combined into one group of 11 control rabbits.

Isolated whole bladder preparation

Under anesthesia, as above, the bladder was exposed via a midline incision and the ureters ligated close to the bladder and cut above the ligature. The bladder and urethra were carefully freed from any fat and connective tissue and excised as close to the pubic bone as possible. The rabbit was then put to death by i.v. administration of 1 ml Beuthanasia-D solution (Schering-Plough).

The bladder was emptied and the urethra cannulated with a saline-filled "J"-shaped platinum electrode-tipped catheter. The same "J" tube, 8.4 cm in length, was used in all experiments. The internal diameter of the "J" catheter and all tubing between the bladder and exit port within the bottle was 3 mm. The intact preparation was mounted in a 300-ml isolated bath chamber containing Tyrode's solution (NaCl 124.9 mM, KCl 2.5 mM, $NaHCO_3$ 23.8 mM, $MgCl_2$ 0.5 mM, NaH_2PO_4 0.4 mM, $CaCl_2$ 3.6 mM, and dextrose 5.5 mM) equilibrated with 95% O_2, 5% CO_2 and maintained at 37°C [18, 19]. Surrounding the bladder in the bath was a cylindrical platinum electrode used for FS. The catheter was connected by a three-way valve to both a pressure transducer (Statham P23XL) connected to a Harvard syringe pump and an exit port connected to an empty lightweight plastic bottle hung from a force displacement transducer (Grass, FT-10E), which could be smoothly raised and lowered on a stable vertical pole.

Determination of capacity and isovolumetric field stimulation

To determine capacity, the bladder was filled with saline at a rate of 1.5 ml/min. Capacity was defined as the volume at twice the plateau pressure [7]. Subsequently, the bladder was emptied. The bladder was then filled successively with 5, 10, and 15 ml saline. In each case, after filling, the bladder was allowed to equilibrate for 15 min, at which time the intravesical pressure was recorded. With the system closed to the exit port, the bladder was stimulated using FS [Biosonics, Moorestown, NJ; 32 Hz (biphasic square wave pulses), 1 ms, 80 V, 10-s train] and isovolumetric pressure was recorded. This level of stimulation produces maximal pressure generation, and 90% of the isometric pressure response can be inhibited by application of tetrodotoxin (1 μM), demonstrating that the response results from neurohumoral stimulation [16]. Intravesical pressure was recorded on a Grass Model 7E polygraph and simultaneously digitized at 5 samples/s on a DX-486 computer via an analog-to-digital data conversion system (Keithley, Soft-500). After each stimulation, the bladder was emptied, refilled to a new volume, and re-equilibrated.

Stimulation to empty

The bladder was filled to 15 ml (chosen because most bladders could empty this volume with FS) and allowed to equilibrate for 15 min. The height of the exit port was set to equal the intravesical pressure so that when the stopcock was opened to allow flow between the bladder and the exit port, no fluid moved either into or out of the bladder. The exit port was then opened and the bladder stimulated. The bladder emptied through the tubing into the plastic bottle suspended from the force transducer, calibrated to measure volume emptied.

To test the emptying ability of the bladder with several forms of stimulation, we repeated the above procedure 3 times using FS, bethanechol (250 μM), and KCl (120 mM). Previous studies have demonstrated that these concentrations produce maximum responses in the rabbit bladder [18, 20, 21]. Since the purinergic component of FS does not contribute to rabbit bladder emptying [22], purinergic stimulation was not included in this study. Intravesical pressure and volume emptied were measured continually and digitized at 5 samples/s (FS) or 3 samples/s (bethanechol and KCl) until the bladder emptied, or the rate of emptying fell to zero. At the end of emptying, the bladder was emptied by gravity to determine the residual volume. The bladder was washed 3 times with fresh oxygenated Tyrode's solution at 15-min intervals after each chemical stimulation.

Data analysis

Maximum rate of pressure increase (isovolumetric study) occurred within the 1st s after electrical stimulation and was calculated by the computer as the maximum slope between two isovolumetric pressure data points (data collected every 200 ms). Mean rate of pressure increase (emptying study) was calculated as maximum pressure divided by the stimulation time to reach maximal pressure.

Flow rate during bladder emptying was obtained by differentiation of the instantaneous volume emptied as described previously [9]. Instantaneous power and external work were calculated from pressure and flow rate. The instantaneous power of the bladder contraction was obtained by multiplying pressure and flow rate at every data point collected. This assumes flow is steady [39], a good approximation for this apparatus with its narrow exit tubing, and for the female human urethra [8, 47]. The mechanical work done by the bladder during emptying was calculated by taking a digital integral of power over the entire emptying time (trapezoid method). Power and work are presented in SI units [milliwatts (mW) and millijoules (mJ), respectively]: $1 cmH_2O \times ml/s = 0.0981$ mW; $1 cm H_2O \times ml = 0.0981$ mJ.

Statistics and drugs

Each set of data represents the mean ± SEM of 5–12 individual preparations. Statistical analysis was done either by *t*-test or by analysis of variance, using the Student-Neuman-Keuls test to compare multiple groups. All drugs used in this study were obtained from Sigma Chemical Co. (St. Louis, MO).

Results

Bladder mass increased and percentage volume emptied decreased significantly among the obstructed animals (Table 1), leading to an inverse relationship between the two (Fig. 1a). Bladder capacity was highly variable among the obstructed animals (Table 1) and there was no relationship between either capacity and percentage volume emptied ($P > 0.05$, Fig. 1b) or capacity and bladder mass ($P > 0.05$, data not shown).

For this study we divided the obstructed bladders into compensated and decompensated groups based on the percentage volume emptied. We defined compensated obstructed bladders as those that could empty 71% of the initial contained volume when stimulated with FS. Those that could not empty 71% were designated decompensated (Table 1, Fig. 1). Seventy-one percent emptied is three standard deviations below the mean percentage volume emptied by the control bladders.

The choice of 71% was arbitrary. Previous separations of bladders between compensated and decompensated were based on bladder mass [16, 26]. Since the terms compensation and decompensation refer to the functional status of the bladder, we chose to base the separation on the functional parameter of bladder emptying. However, both methods of distinguishing between compensation and decompensation give virtually the same results and are equally arbitrary.

With the obstructed bladders divided in this manner, only the decompensated bladders showed a consistent significant difference from the controls in the isovolumetric FS study (Fig. 2). At every volume tested, the decompensated bladders produced significantly less pressure and were significantly slower to contract than either the controls or the compensated bladders. The maximum isovolumetric pressure of the compensated bladders was greater than that of the controls at all three volumes.

In the emptying study, FS generated a greater maximum intravesical pressure and a faster pressure rise than either bethanechol or KCl in control and obstructed bladders (Fig. 3). The compensated bladders generated the same maximum pressure as the control bladders when stimulated with FS or bethanechol. However, when stimulated with KCl, they generated less than half the maximum pressure of control bladders. In contrast, the decompensated bladders generated less than half the maximum pressure of the control bladders with all three methods of stimulation (Fig. 3a). In addition, the compensated obstructed bladders were able to maintain the same mean rate of pressure rise as the control bladders, with all methods of stimulation, but the decompensated bladders were not (Fig. 3b).

The high pressures generated by FS lead to rapid emptying and higher maximum flow rates than with bethanechol or KCl. Similar to the effect on pressure generation, the compensated bladders were able to maintain the same maximum flow rate as the controls with all methods of stimulation. In contrast, the decompensated bladders had significantly decreased flow rates with all three methods of stimulation (data not shown).

By definition, the compensated bladders emptied the same percentage volume as the controls when stimulated

Table 1 General characteristics of obstructed bladders
* Significant difference with respect to control bladders, $P < 0.05$
\+ Significant difference with respect to compensated obstructed bladders, $P < 0.05$

	Control ($n = 11$)	Obstructed ($n = 17$)	Compensated ($n = 5$)	Decompensated ($n = 12$)
Bladder mass (g)	2.12 ± 0.11	7.68 ± 0.82*	4.88 ± 0.72*	8.84 ± 0.95*,+
Capacity (ml)	47.3 ± 3.5	70.4 ± 9.2	52.2 ± 15.2	78.0 ± 11.0
Percentage volume emptied	94.6 ± 2.3	55.9 ± 7.4*	93.1 ± 3.1	40.5 ± 6.0*,+

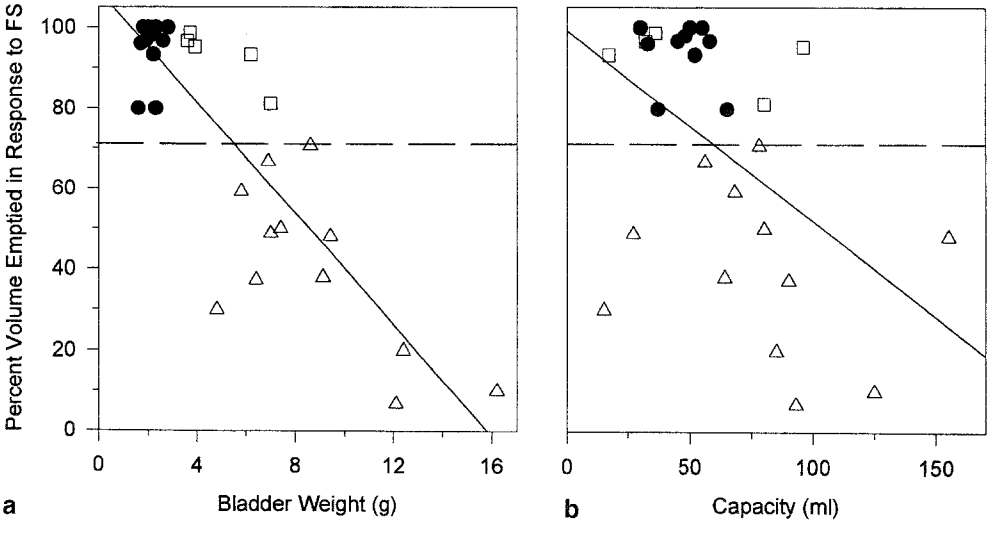

Fig. 1a, b Effect of partial outlet obstruction on bladder mass, capacity, and volume emptied in response to 32 Hz field stimulation. **a** Percentage volume vs bladder weight. A regression line fits the data with $r^2 = 0.74$ (*solid line*). **b** Percentage volume vs capacity. A regression line fits the data with $r^2 = 0.25$ (*solid line*). Each symbol represents one bladder. *Filled circles* represent control bladders. Compensated obstructed bladders (*open squares*) emptied 71% or more of the initial volume (*dashed line*). Decompensated obstructed bladders (*open triangles*) emptied less than 71% of the initial volume

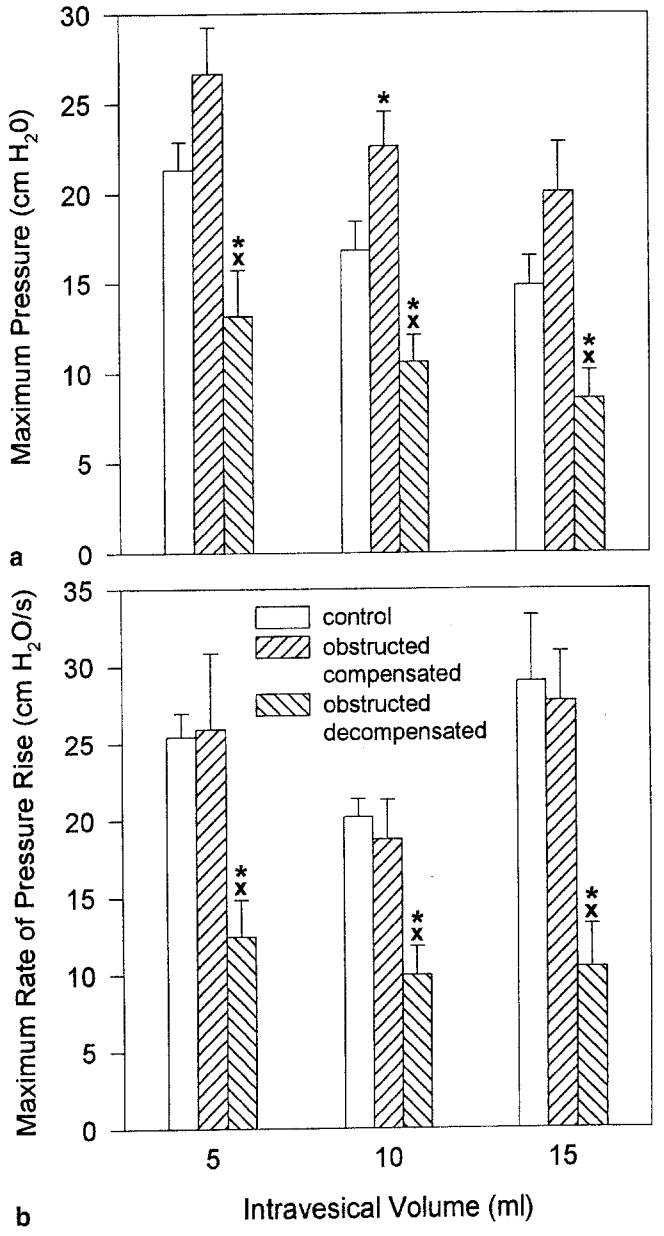

Fig. 2a, b Effect of partial outlet obstruction on isovolumetric contractions in response to 32 Hz field stimulation with 5, 10, and 15 ml intravesical volume. **a** Maximum isovolumetric pressure. **b** Maximum rate of isovolumetric pressure increase. *Each bar* represents the mean ± SEM of 11 control, 5 compensated, and 12 decompensated bladders. *Significantly different from control, ^{X}significantly different from compensated, at $P < 0.05$

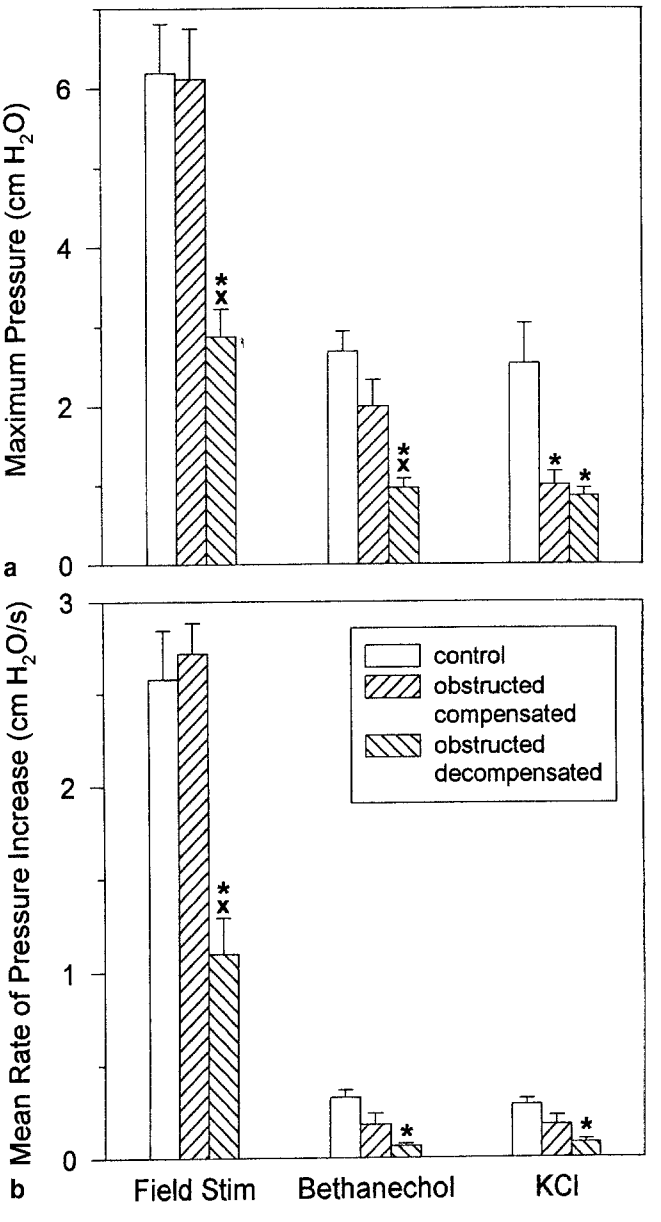

Fig. 3a, b Effect of partial outlet obstruction on the pressure response to field stimulation, bethanechol, and KCl during emptying with 15 ml initial intravesical volume. **a** Maximum pressure during emptying. **b** Mean rate of pressure increase during emptying. *Each bar* represents the mean ± SEM of 11 control, 5 compensated, and 12 decompensated bladders. * Significantly different from control, ^{X} significantly different from compensated, at $P < 0.05$

with FS (Fig. 4). In addition, they could empty the same volume when stimulated with bethanechol. In contrast, the percentage volume emptied by the compensated bladders stimulated by KCl was 30% lower than that of controls stimulated with KCl. The percentage volume emptied by the decompensated bladders was significantly reduced with all forms of stimulation (Fig. 4).

FS generated the greatest power of all forms of stimulation (Fig. 5), as calculated from pressure and flow rates. Maximum power generated by FS was over 4 times greater than for either bethanechol or KCl. The compensated bladders were able to generate nearly the same maximum power as controls in response to FS. Although the power generated in response to bethanechol and KCl was slightly reduced in this group, it did not reach statistical significance. However, the decompensated bladders generated less than 40% of the power of control bladders with all forms of stimulation, a significant reduction (Fig. 5).

The total work performed was significantly reduced in the decompensated bladders with all methods of stimulation (Fig. 6). In addition, the compensated

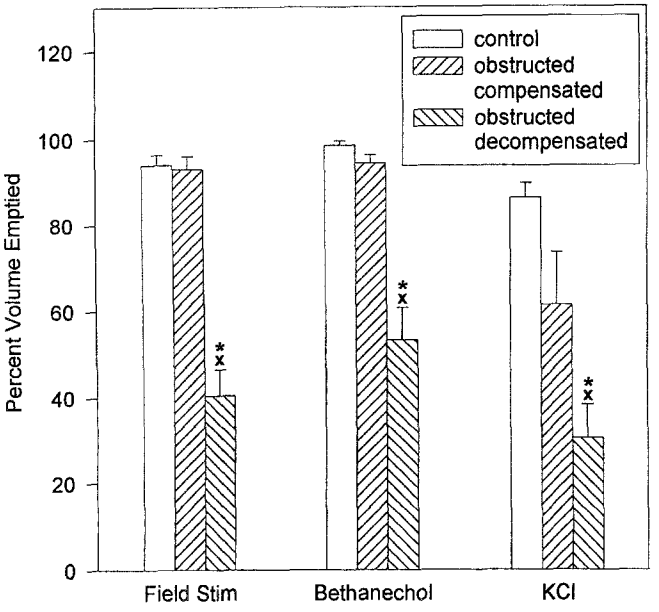

Fig. 4 Effect of partial outlet obstruction on percentage volume emptied in response to field stimulation, bethanechol, and KCl with 15 ml initial intravesical volume. *Each bar* represents the mean ± SEM of 11 control, 5 compensated, and 12 decompensated bladders. * Significantly different from control, ^{X} significantly different from compensated, at $P < 0.05$.

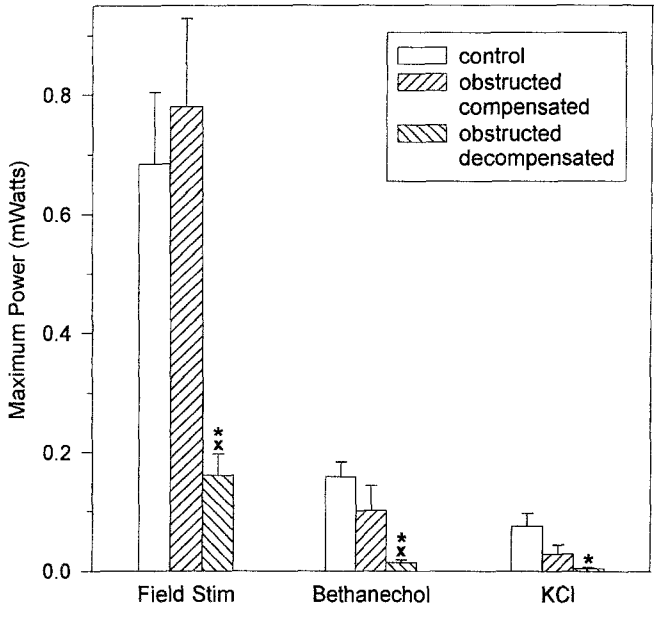

Fig. 5 Effect of partial outlet obstruction on maximum power generation in response to field stimulation, bethanechol, and KCl during emptying with 15 ml initial intravesical volume. *Each bar* represents the mean ± SEM of 11 control, 5 compensated, and 12 decompensated bladders. * significantly different from control, ^{X} significantly different from compensated, at $P < 0.05$

bladders performed less work than controls when stimulated with bethanechol or KCl.

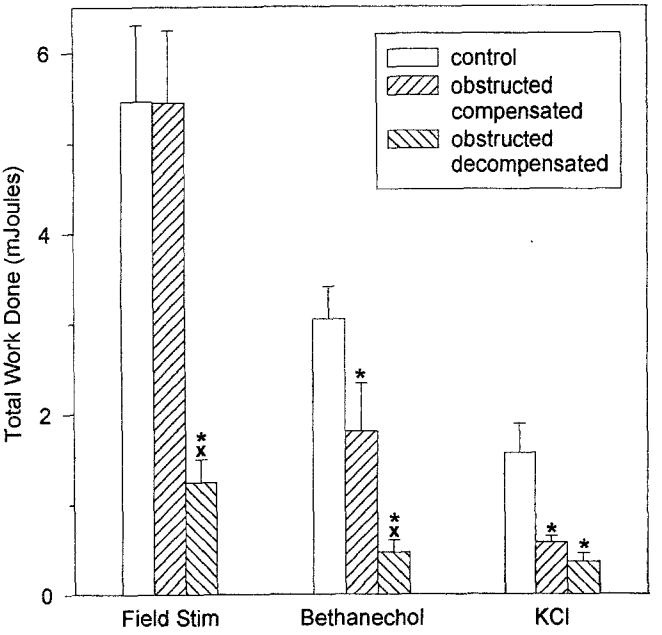

Fig. 6 Effect of partial outlet obstruction on total work performed in response to field stimulation, bethanechol, and KCl during emptying with 15 ml initial intravesical volume. *Each bar* represents the mean ± SEM of 11 control, 5 compensated, and 12 decompensated bladders. * Significantly different from control, ^{X} significantly different from compensated, at $P < 0.05$

Discussion

The urinary bladder collects urine at low intravesical pressures and expels it via a highly coordinated contraction [3, 44, 48]. In rabbits, the micturition contraction consists of both muscarinic and purinergic components [22]. However, even though both muscarinic and purinergic components participate in the phasic response to stimulation, only the muscarinic stimulation is involved in the tonic portion, which is responsible for bladder emptying [22].

The dynamics of isometric field-stimulated contraction show that the initial response is characterized by a rapid rise in pressure to a peak followed by a decay of intravesical pressure to a relatively stable pressure. During emptying, as long as the intravesical pressure during the stable period is greater than the outlet resistance, the bladder empties completely. Partial outlet obstruction alters the response such that intravesical pressure decays below the outlet resistance before empyting is complete. Because of the dynamics of the pressure decay following peak pressure, flow rate, power, and work cannot be calculated based on peak pressure, but must be integrated over the period of stimulation.

The calculations of work and power do not reflect that bladder smooth muscle expends considerable energy on the isometric generation of pressure in the absence of fluid flow [23, 25, 40]. However, as mentioned above, the ability of the bladder to generate isometric pressure

is not an accurate measure of the ability of the bladder to empty. In many clinical situations (e.g. obstructive disorders, bladder-sphincter dyssynergia), as well as experimentally (e.g. partial outlet obstruction, unilateral ischemia), the bladder is capable of generating normal intravesical pressure although bladder emptying is significantly impaired [16, 26, 31, A. J. Wein, 1996, personal communication]. In these cases, the objective measurement of mechanical power and work may provide important information.

This study utilized three forms of smooth muscle stimulation to localize the defects in contraction that occur after an outlet obstruction. FS acts through the release of neurotransmitters [16]. Bethanechol is a direct muscarinic agonist, and KCl stimulates contraction by directly depolarizing the smooth muscle. In both control and obstructed bladders, FS contracted the bladder fastest and most powerfully. It generated the highest pressures, the fastest flow rate, the greatest power, and the highest mechanical work (Fig. 3–6). In contrast, KCl emptied the bladder at the slowest rate, generated the lowest power and the least work, and emptied the smallest volume.

This difference may be explained by consideration of the source of calcium utilized by the different methods of stimulation. KCl-stimulated contraction is mediated primarily, if not solely, by extracellular influx through voltage-operated, dihydropyridine-sensitive channels [33]. On the other hand, receptor-stimulated contraction (as by FS or bethanechol) is mediated by a combination of extracellular calcium influx and calcium release from intracellular sites [4, 13, 17, 28, 29, 32, 37]. Since calcium release from intracellular sites occurs faster then diffusion from extracellular sources, contractions generated by FS and bethanechol occur faster than those generated by KCl. In addition, since FS and bethanechol stimulation take advantage of more sources of calcium than KCl stimulation, these generate more powerful contractions.

Partial outlet obstruction results in rapid enlargement of the bladder. In rabbits this consists of smooth muscle hypertrophy, connective tissue synthesis, and urothelial and fibroblast hyperplasia [24, 27]. Functionally, the response of the bladder can be divided into two categories. Compensated bladder function occurs when the enlarged bladder functions relatively normally. Decompensated function occurs when there is a decrease in the ability of the bladder to generate and sustain pressure, and to empty [24, 27].

In most previous studies, bladder weight has been used to determine if obstructed bladder function is compensated or decompensated [16, 26]. In this study we used percentage volume emptied in response to FS, since that is the most direct in vitro physiological correlate of bladder function. Our choice of a statistical measure to divide compensated and decompensated obstructed bladders results in a similar distribution between compensated and decompensated rabbits to that produced using bladder weight [16, 34].

Similar to previous studies [16, 26], there was a close inverse relationship between bladder weight and volume emptied (Fig. 1a), so it would have sufficed to classify the bladders by their weight had the volume emptied not been available (such as in bladder strip studies). However, selecting an appropriate bladder weight is not obvious. For example, a limit of 4 g classifies all obstructed bladders as decompensated, while a limit of 5 g includes one bladder that could only empty 30% of its initial volume in the compensated group.

It is interesting to note that capacity cannot suffice as a useful indicator of the ability of the bladder to empty (Fig. 1b). There was a great variation in bladder capacities, and no relationship between capacity and bladder mass, or between capacity and percentage volume emptied.

One could argue that the compensated bladders were incompletely obstructed. The surgical procedures for producing obstruction were done by the same surgeon using a consistent technique. However, as has been reported previously, the increase in bladder weight after experimental obstruction in rabbits is variable [16]. This is also true in rats [35, 41, 42] and guinea pigs [38, 46], and is probably due to an inherent variability in the responsiveness of bladders from different animals to obstruction, similar to the variable development of obstruction in humans.The compensated group were obstructed and had significantly increased bladder mass when compared to the controls (Table 1). They therefore could represent an experimental group comparable to patients with mild unsymptomatic BPH.

Compensated bladders weigh significantly more than control bladders, and previous work has shown that most of this increase in weight is composed of smooth muscle [5]. They therefore have a thicker bladder wall and thicker smooth muscle layer at the same contained volume. Although the compensated bladders generate higher isovolumetric pressures (Fig. 2a), they perform less work when stimulated with bethanechol and KCl than control bladders (Fig. 6). Therefore, although the contractile ability of the compensated bladders is not reduced, as shown by isovolumetric contractions, their ability to do work and empty is reduced.

When stimulated to empty with KCl, the compensated bladders generated less than half the maximum pressure, performed less than half the work, and emptied 30% less volume than the control bladders, although this value did not reach statistical significance (Fig. 3, 4, 6). In contrast, the decompensated bladders showed significant reductions in their ability to contract isovolumetrically (Fig. 2) and to empty with all three forms of stimulation: they generated 40% of the power of control bladders and performed 20% of the work (Figs. 5, 6).

The contrasting results between compensated and decompensated obstructed bladders suggest that they represent two different dysfunctions. The reduction in the response of the compensated bladders to KCl indicates that the defects in these bladders could be related to the direct interaction of the smooth muscle proteins

with calcium and ATP, rather than changes in neuronal innervation or muscarinic receptors and second messenger systems. One possible scenario is that as the bladder enlarges due to smooth muscle cell hypertrophy, there is a greater distance between the voltage-sensitive calcium channels and the smooth muscle proteins, resulting in increased time for diffusion of calcium. Since the response to KCl stimulation is highly dependent on extracellular calcium [33], the increased diffusion time would result primarily in a decreased response to KCl. There may be a compensatory increase in calcium-induced calcium release from the sarcoplasmic reticulum, resulting in an increased response to FS and bethanechol, and explaining the observed results for the compensated obstructed bladders.

The decompensated bladders represent a more dysfunctional group and respond poorly to all forms of stimulation. This suggests that the degenerative processes within the bladder may be directly related to cellular damage to metabolic processes involved in energy synthesis, storage, and utilization. Metabolic studies have demonstrated that mitochondrial function (represented by oxygen utilization, ATP synthesis, and specific mitochondrial enzyme activity) is significantly reduced by partial outlet obstruction [12, 14, 15].

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