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# Effect of Alpha-adrenergic Blockade and Anticholinergic Agents on the Decentralized Primate Bladder

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The effect of anticholinergic and alpha-adrenergic blocking agents on the primate bladder decentralized at the sacral level was studied. Both agents diminish the intravesical pressure response to filling and slightly increase capacity. Each appears to exert an independent effect.

**Key words: anticholinergic agents, alpha blockade, decentralized primate bladder**

## INTRODUCTION

A corrective effect of alpha-adrenergic blocking agents on ureteral dilatation has been reported [Stockamp, 1975; Stockamp and Schreiter, 1973]. While this effect could be related to decreased bladder outlet resistance, there are circumstances where that seems unlikely to be the explanation. The preganglionically denervated bladder which coexists with a nonfunctional internal but active skeletal sphincter encounters urethral resistance in the area of the pelvic diaphragm, an area not influenced by alpha blockade [McGuire et al, 1981; McGuire, 1977].

Sundin and Dahlstrom [1973] and Sundin and co-workers [1977] reported an increase in alpha-adrenergic receptor sites in the decentralized cat and human detrusor and a change from the predominance of beta-adrenergic (relaxation) function to a predominance of alpha-adrenergic (contraction) function during bladder filling. The decreased bladder compliance which develops after sacral level decentralization may thus be partially an alpha-adrenergic-receptor-mediated influence. That portion of decreased compliance related to alpha-adrenergic receptor activity should be blocked by phenoxybenzamine, and a possible portion due to cholinergic influences should be blocked by anticholinergic agents. To study these relationships, seven female crabeater monkeys (weight 26–52 kg) were evaluated urodynamically before and at 6 weeks after intradural rhizotomy performed from L5 through S4.

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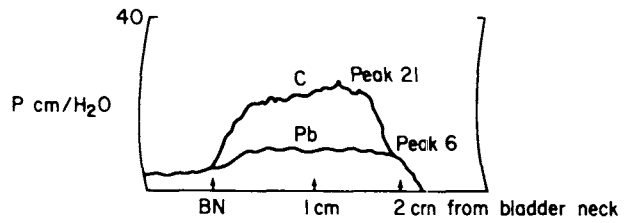


Fig. 1. Urethral pressure profilometry in decentralized monkey measuring 21 cm of water in the proximal 1–2 cm of urethra (C) with superimposed repeat profilometry after the administration of 2 mg of phenoxybenzamine (Pb) intravenously, demonstrating a decrease in urethral closing pressure to less than 6 cm of water.

## NEUROSURGICAL METHODS

After Ketaset sedation, general endotracheal anesthesia was induced with halothane and $O_2$ and a lumbosacral laminectomy was performed. The fifth lumbar through fourth sacral roots were divided within the dural canal with the aid of an operating microscope. All of the roots were completely sectioned. Following operation, the monkeys were managed by Crede voiding on a b.i.d. basis.

## URODYNAMIC METHODS

Under Ketaset sedation, urethral closing pressure profiles were performed using a 5 French feeding tube with a single lateral perfusion aperture. The urethral catheter was perfused with a Harvard syringe pump at 2 ml per minute. Cystometrograms were performed via an 8 French Foley catheter with a 3-cc balloon inflated to occlude the bladder outlet. Bladder filling was induced with a Harvard syringe pump at 6 ml per minute. Intravesical pressures and urethral closing pressure profiles were measured via a side-arm tube, a P23A Statham pressure transducer, and recorded on a Grass polygraph. Transvaginal placement of two #30 Grass monopolar needle electrodes was used to measure urethral sphincter EMG activity.

## RESULTS

Urodynamic evaluations performed 6 weeks after rhizotomy revealed no skeletal sphincter activity as determined by EMG recordings with residual smooth-muscle closure of the proximal urethra measuring a peak of 20 ($1 \pm 5$) cm of water (Fig. 1). Cystometrograms performed via a Foley catheter showed hypertonic areflexic bladder pressure filling curves (Fig. 2). Administration of phenoxybenzamine (2 mg intravenously) flattened the intravesical pressure response to filling and increased capacity slightly. At capacity, a sharp rise in intravesical pressure occurred in the control and the phenoxybenzamine-treated animals (Fig. 2). Urethral pressure profiles performed subsequent to phenoxybenzamine injection showed a marked decrease in peak urethral closing pressure (Fig. 1).

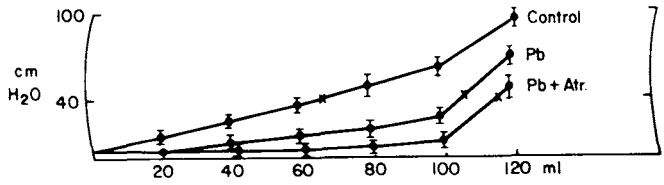


Fig. 2. Recordings of intravesical pressure response to bladder filling at 20 ml/min in decentralized monkey. Control studies show a continuous rise in bladder pressure with filling reaching 40 cm of water at a 60-ml bladder volume. The administration of phenoxybenzamine (Pb) (2 mg intravenously) results in a bladder pressure curve that remains at less than 20 cm of water until a bladder volume of 100 cc is reached, at which time intravesical pressure rises sharply. After the administration of phenoxybenzamine (Pb) (2 mg intravenously) and atropine (.25 mg intravenously), intravesical pressure remains below 20 cm of water to a bladder volume of 100 ml when bladder pressure rises sharply.

The administration of both phenoxybenzamine and atropine (.25 mg intravenously) prolonged the low pressure vesical response to filling and increased capacity as compared to the findings of those animals treated with phenoxybenzamine alone or the control situation (Fig. 2). Depression in the intravesical pressure response to filling up to capacity was more marked when both drugs were used concurrently.

## DISCUSSION

In a prior report we described the evolution of neurogenic vesical dysfunction after experimental sacral rhizotomy with resultant partial vesical decentralization [McGuire et al, 1982]. The changes include a loss of skeletal sphincter activity and the gradual development of a hypertonic bladder. While vesical capacity after decentralization is greater than in normal animals, or those with suprasacral spinal cord injury, intravesical pressures for a given volume are higher.

In the female monkeys studied here, vesical wall thickening and trabeculation occurred universally, but upper tract deterioration at least by gross examination of the ureters did not. This appears to be related to low urethral resistance with a peak pressure of 20 cm of water in these animals. Occlusion of the vesical outlet with a Foley catheter permits assessment of the intravesical pressure response to filling and obviates the influence of alpha-adrenergic blocking agents on urethral closing pressure exerted by smooth musculature. In this circumstance, both phenoxybenzamine and atropine when given separately diminished the intravesical pressure response to filling and increased bladder capacity. When both agents were given together, a more pronounced shift of the pressure volume curve to the right occurred.

The relationship between intravesical pressure and ureteral resistance to perfusion has been shown clinically and experimentally [McGuire et al, 1981; Coolsaet et al, 1982]. Intravesical pressure has a direct parallel effect on ureteral resistance which is particularly noticeable after decentralization, since the bladder pressure rise with filling is steady and progressive. Adverse ureteral effects are seen clinically if the "denervated" bladder must achieve a pressure of 40 cm of water or more to induce urethral urinary flow. To protect the ureters from intravesical pressure, intermittent catheterization can be combined with anticholinergic agents which have a direct effect

on bladder "tone." Alpha-adrenergic blockade could diminish vesical pressure with filling by two possible modes of action. Alpha-adrenergic blockade diminishes urethral resistance and could lead to urethral urinary loss at a lower bladder pressure, provided the "external sphincter" were nonfunctional. In addition, phenoxybenzamine appears to diminish intrinsic vesical tone after decentralization. The net effect of administration of either phenoxybenzamine or atropine was a decrease in intravesical pressure at a given volume until capacity was reached, at which time bladder pressure rose steeply. It appears that vesical capacity is partly limited by the viscoelastic properties of the bladder wall, but that either or both of these agents have an effect on intrinsic detrusor tone. Our results suggest that the portion of intravesical pressure which is influenced by these drugs is the result of a neuromuscular process, and not simply collagen deposition and mural fibrosis. Clinically, a decentralized bladder fills and gains pressure until urethral resistance is overcome and urinary loss occurs. There are two problems with this kind of lower urinary tract dysfunction: incontinence and an adverse effect on ureteral function. Since intravesical pressure is related to volume, simply decreasing urethral resistance which allows urine flow at a lower volume can reduce ureteral dilatation. This, of course, makes incontinence worse. Alternatively, this kind of dysfunction may be treated by intermittent catheterization, in which case it is important to diminish intravesical pressure as much as possible to prevent incontinence, as well as to prevent adverse effects on ureteral function. It seems likely that alpha-adrenergic blockade in those individuals with *only* a functional internal sphincter, and no skeletal sphincter function, might well aggravate incontinence due to its effect on the smooth sphincter. In the typical myelodysplastic patient with no internal sphincter function, and a relatively high pressure skeletal sphincter, any method to decrease intravesical pressure and facilitate storage would be helpful both for continence and to protect the ureters. Alpha-adrenergic blockade would not further influence urethral resistance. In those patients with areflexic vesical dysfunction selected for an artificial sphincter, both alpha-adrenergic blockade and anticholinergic therapy may be useful to diminish vesical pressure responses to filling, as well as to diminish intrinsic outlet resistance.

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